PSSD, PFS, PRSD: Aetiology and Treatment

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This paper constitutes the presentation of a theory regarding the cause and treatment of PSSD,PFS and PRSD. Presentation of known data and factual observations will precede speculation as to aetiology and treatment. All speculations are backed by scientific literature. However, lack of direct evidence and sufficient studies necessitate indirect conclusions. A simple, inexpensive and safe treatment is nevertheless proposed. To the best of the author's knowledge no similar collections of thought have been considered. An attempt to explain the thought process behind each deduction has been made.

Introduction

What makes a good theory?

- **Logical consistency, coherence**
- **Ability to predict outcomes and explain already known phenomena**
- **Falsifiability**
- **Parsimony**

I kept these four basic concepts in mind as I went along. I adjusted my theory to the facts and not the facts to my theory, made sure the same reasoning applies throughout the entire thought process and at no time contradicts itself, avoided uneconomical and unnecessarily complicated explanations and multiplications, and found no evidence to this point of my approach having been tried before and failed - but remained strict with the criteria of what would constitute that failure. These concepts served as guiding lights in connecting the dots and were relied upon whenever the theory needed to be adjusted. I developed this theory via a compilation of anecdotal evidence and reports coupled with extensive reading of the scientific literature regarding the topics at hand and their peripheries. Although there exists comparatively little to no research on PSSD directly, most of the ideas and thought processes presented in here are well documented and known. Published evidence served as a mandatory catalyst for connecting each point to the next. In other words, though the theory remains fundamentally speculative, no arbitrary leaps of faith have been taken nor baseless assumptions made.

References will be provided for scientific research that supports each argument, but the sum of these references will only point to a subset of the total literature studied. The references for the more speculative parts of the theory will be more carefully attended to than those for the already well understood facts and definitions.

References for anecdotal reports and evidence will be provided when deemed significant and will serve as examples not indicative of the sum of anecdotal reports on any certain claim. Confirmation of anecdotal evidence can be found at the PSSD subreddit and other PSSD communities online.

The theory

Laying the groundwork

PSSD, PRSD and PFS symptoms include major sexual, cognitive and emotional dysfunction. Additional symptoms are reported to varying degrees. Keeping these in mind is essential in order to remember that whatever is causing the syndrome is likely the direct or indirect cause of both major and minor symptoms. Hence, we will focus in the three major categories which are always reported, hold the most gravity and seem to be at the core of the issue. Additionally, though some similar symptomatology may be experienced *during* administration of the drug, the full syndromes only manifest after *discontinuation* of it, and correlation between these two states is not necessary.

PSSD is diagnosed only after symptoms persist months after discontinuation. It is thus reasonable to assume that PSSD is not caused due to the direct presence of the medication in the body, but rather due to ways in which the medication chronically influenced certain mechanisms.

Further observations include:

1) Among PSSD sufferers there are reports of occasional windows of recovery, which may last from days to (rarely) a few weeks, without taking any noteworthy action, before going back to their usual PSSD state.
2) Some patients make a full recovery over varying amounts of time.
3) The dose and duration of SSRI treatment is not necessarily indicative of either the appearance or the severity of the syndrome. PSSD has been reported to appear even after only a single therapeutic dose of an SSRI.
4) Some degree of temporary symptom alleviation with reinstatement of an SSRI is widely reported. There even exist accounts who claim to have fully cured PSSD with reinstatement, even after second discontinuation of the SSRI[1]. However, most of those who reinstate merely return to usual symptomatology after once more discontinuing the medication, or end up in a worsened condition.

The above observations allow for important assumptions:

- PSSD is likely reversible. The mechanisms necessary for normal sexual, cognitive and emotional function may still be present, functional, and not irreversibly destroyed.
- PSSD is less likely to be related to chronic adaptations and long-term systemic exposure to toxicity, and more likely to be related to acute systemic adaptations that remain upon SSRI discontinuation.
- The direct and indirect effects of SSRIs are crucial in order to understand not only what provokes the syndrome but also what provokes recovery. It is thus not impossible, that PSSD is due to some imbalance, adaptation or dysregulation, which is corrected to a certain albeit minor degree upon reinstatement, and once again thrown off after cessation. This allows for the possibility of PSSD arising due to protective homeostatic mechanisms instead of directly induced neurotoxicity.

There are three known groups of people complaining of near identical symptomatology after ingesting and then stopping three different types of drugs.

1) PSSD is chronic major sexual, cognitive and emotional dysfunction caused by SSRIs, SNRIs and some tricyclic antidepressants.
2) PFS is chronic major sexual, cognitive and emotional dysfunction caused by Finasteride.
3) PRSD is chronic major sexual, cognitive and emotional dysfunction caused by Isotretinoin.

Three separate iatrogenic conditions that present in the same manner across very different people who took dissimilar medications, towards entirely different goals. Major symptoms are essentially identical in all three, and more specific symptoms or comorbidities vary.

Though the similarity of presentations is obvious, these conditions have remained for the most part distinct and tackled separately, as there has been no clear reason to consider them as one. In this paper, I propose that these three disorders are actually identical in aetiology, presentation and treatment. To provide the bridge for this connection, I will present a fourth group of patients, displaying the exact same symptomatology, once again through an entirely distinct pathway. I will subsequently explain how the fourth group is connected to the others, and how that information leads to conclusions on resolution of the syndromes.

The fourth syndrome

The fourth group consists of people who have experienced identical and equally permanent symptomatology after administration of varying doses of Aromatase Inhibitors (AIs). This syndrome will be referred to as Post AI Major Dysfunction (PAMD) for lack of any previously given name. (Differentiation to hypoestrogenism will be explained soon.)

AIs are used in breast cancer patients for the treatment of breast cancer. They are also used off label in men for the treatment of gynecomastia[2]. Furthermore, they are used by people who engage in Androgenic Anabolic Steroid(AAS) use for performance enhancing reasons. They work by inhibiting aromatase, an enzyme that is vital for the conversion of Testosterone(T) to Estradiol. Aromatase will be discussed further later.

By inhibiting aromatase, AIs indirectly decrease the levels of estrogens, and at the same time indirectly increase the levels of androgens. This effect is further pronounced in males, whose total estrogen levels are heavily dependant on this process and have little to no natural production of estrogen, whereas females produce the majority of estrogens directly in the ovaries. There are three major endogenous estrogens that that have estrogenic hormonal activity: estrone(E1), estradiol(E2), and estriol(E3). **Estradiol(E2)** is the prevalent and most potent estrogen, and the only one with a major role in males.

It would be reasonable to assume that AI overuse leads to medication-induced hypoestrogenism, the effects of which are relatively well understood. It is treated with low dose estrogen medications in women, and Testosterone Replacement Therapy(TRT) or simple cessation of AIs in men. Serum estradiol levels quickly return to normal and symptoms cease. However, PAMD does not resemble hypoestrogenism. PAMD begins abruptly. It is reported to arise from a severe, acute drop in estradiol after ingestion of high dose AI, down to the point of being undetectable or close to 0 on sensitive E2 blood tests. It is unclear how long such low levels need to be maintained in order to provoke PAMD, but severity of deprivation seems to be more important than duration, based on available anecdotal reports. Without this severe drop, PAMD never arises even with long-term AI use. Full symptomatology appears within a few days since presentation of initial symptom and cessation of AI and remains chronically unchanged. Unlike hypoestrogenism, PAMD does not resolve with return of estradiol levels to normal. It is unresponsive to TRT or AI cessation. Symptoms differ significantly and PAMD only fully manifests after discontinuation of AIs and persists. Sufferers report little to no improvement over time.

Reported symptoms of PAMD include:

Severe anxiety	Anhedonia
Major Depression	Fatigue
Complete loss of libido	Irritability
Erectile Dysfunction	Cognition, memory and concentration issues
Genital numbness	Reduced muscle size and response to exercise
Muted orgasms	Reduced vascularity and cardiovascular ability
Reduction in testicle and penile size	Dry skin
Reductions in seminal volume and change in texture	Scalp hair loss
Apathy	Inability to sweat / severely reduced sweating
Emotional numbness	Changes in body odour
Loss of motivation	Frequent urination / Pelvic floor dysfunction
Intense Brain fog	Depersonalisation
Smell and taste changes	Vision problems

Figure 1. Reported symptoms of PAMD

The most severe and consistent symptoms consist of sexual, cognitive and emotional dysfunction, and the less consistent symptoms vary between individuals. The nature of PAMD makes it extremely rare. Its appearance is limited to the below settings, in order of frequency:

1. Medically unsupervised AAS abuse
2. Medically unsupervised TRT.
3. Medically supervised TRT.

PAMD as defined above remains unknown to the scientific community. As a result, all available reports are anecdotal. However, reports are predictable in symptomatology, aetiology and duration, so much so that these characteristics can be tied to the direct effects of an “AI overdose”. These cases and their characteristics are dissimilar to all other problems faced by men on TRT or AAS in general.There are anecdotal reports of PAMD persisting for longer than 4 years, as seen in AAS and TRT forums.

PAMD is always severe, but to varying degrees. The same issues and similar severity have been reported across a wide range of doses. This betrays some individual-specific predisposition or sensitivity that may increase the chances of the syndrome appearing.

All claims regarding PAMD made in this document can be observed in the anecdotal reports in these two threads, but are not limited to these two threads alone:

Low E2 symptoms didnt go away after crash - excelmale.com

Can estrogen crash cause desensitization/knock out of the estrogen receptor - lets discuss! - excelmale.com

Correlation and causation - How AIs cause PAMD

Unlike the other three syndromes, PAMD offers the advantage that cause and effect are easy to see. As discussed, the function of AIs is to reduce Estradiol levels in the blood. PAMD appears following AI overdose and subsequent elimination of Estradiol levels. It follows that **PAMD is provoked by acute elimination of serum estradiol levels.** However, it can be argued that provocation of PAMD by AIs points directly to aromatase inhibition as a mechanism, or toxicity induced by AI ingestion being the culprit instead.
Let us test the argument from our current understanding:

1. As previously mentioned, long-term AI treatments are commonly used in both males and females for various medical reasons. Though they come with known short and long-term side effects, this presentation has not been reported after discontinuation. This points away from long-term toxicity exposure.
2. Although the side effects of AI-induced severe Estrogen deprivation in breast or uterine cancer patients are very similar to PAMD, they resolve upon discontinuation of the medications. This points away from permanent effects resulting directly from aromatase inhibition.
3. PAMD most often appears acutely, after short term AI exposure and can appear with a single dose of sufficiently-dosed AI. This also points away from long-term toxicity exposure.
4. Estradiol levels return to normal after cessation of AIs. This points away from direct or permanent alterations in aromatase secretion or the ability of aromatase to produce Estrogens.
5. The only other setting where identical symptoms present is in chronically Estrogen deprived cancer patients who are undergoing AI treatment. This further connects PAMD to severe Estrogen deprivation.

The fourth observation contradicts our assumption. If PAMD is directly caused by the drop in E2 levels, then it should resolve once they return to normal. Sufferers in the online discussions theorised that could betray a rapid adaptation of the endocrinological mechanisms to the adverse conditions of extremely low E. As a result, otherwise “normal” levels could actually be too high. Consequently, they reported trying to take an AI once again to test that possibility. Instead of providing any relief, it worsened the syndrome. But if less Estradiol worsened the condition, is it safe to assume more will improve it?

Indeed, continuing further down the reports of PAMD, we eventually find attempts to supplement with Estradiol Valerate, despite their blood work showing normal, even higher than normal levels of Estradiol already. This intervention would not have been suggested by any clinician following the guidelines of any endocrinology association. And yet, exogenous estradiol supplementation immediately provided significant symptom alleviation. So much so that at least 3 distinct reports of attempted Estradiol supplementation in the same thread all enjoyed the same results. Another interesting point, is that finasteride also provided significant symptom relief to two PAMD sufferers, before they attempted exogenous estradiol. Just as supplementing with Estradiol directly

increases E2 levels, finasteride indirectly does the same by inhibiting 5a-reduction. This results in reduced Dihydrotestosterone(DHT) levels and higher available Testosterone which subsequently leads to higher aromatisation, increasing E2.

Let us then initially quickly examine whether estradiol presence is important enough so that its deficiency cause these symptoms, before diving more deeply into the specific mechanisms.

The role of Estradiol in male physiology

Estrogen function is a vast topic, still rapidly evolving in endocrinology. Estrogen was initially not thought to be of much significance in males, as estrogens have been considered predominantly female hormones, while testosterone and its androgenic derivative Dihydrotestosterone(DHT) are thought dominant regarding male attributes and sexual function. For this reason, low levels of estradiol were believed to be optimal in males, and TRT protocols in the last two decades widely focused on maintaining as little estradiol concentrations as possible, in order to optimise sexual and cognitive function as well as muscularity, and other aspects that have been associated with the influence of androgens on the male body. More recently however, estradiol has been gaining importance as a regulatory hormone in all aspects of male function. A few relevant points are outlined below:

- Estrogen receptors(ERs), as well as aromatase, the enzyme that converts testosterone to estrogen, are abundant in brain, penis, and testis, organs important for sexual function.[5]
- In the brain, estradiol synthesis is increased in areas related to sexual arousal[5].
- In the penis, estrogen receptors are widespread in high concentrations[5].
- In the testes, spermatogenesis is modulated at every level by estrogen, starting with the hypothalamus-pituitary-gonadal axis, followed by the Leydig, Sertoli, and germ cells, and finishing with the ductal epithelium, epididymis, and mature sperm[5].
- Estrogen can sustain libido as well as affect the amount of serotonin receptors in the brain modulating mood, mental state, cognition, and emotion[5].
- Estrogen can be synthesized in the brain by the enzyme aromatase providing a source of locally high concentrations of the steroid[5].
- A role for rapid changes in estrogen production in the central nervous system is supported by experiments showing that acute aromatase inhibition affects nociception as well as male sexual behavior and that preoptic aromatase activity is rapidly (within min) modulated following mating[5].
- Estrogen has strong ties to areas of the brain regulating anxiety, depression[6].
- Estrogen receptors are present in tissues involved in sexual behavior including several brain centers and pelvic floor muscles. Exogenous estrogens can restore some sexual interest to greater than castrate level in castrated animals[7]. This has also been reported for patients undergoing androgen deprivation therapy who take exogenous

estrogens and others who are on high dose antiandrogens which increase endogenous estradiol levels. [7]

- Different levels of estradiol are correlated with sexual dysfunction in adult men[9]
- Estrogen has been linked to memory function in aging men[10].
- Anti-androgen treatment by blocking the androgen receptor(AR) with Flutamide and thus allowing for more aromatisation, interestingly showed an increase in the number of ex copula erections in castrated rats[7], displaying a potential role of estrogen in erections.
- Both Testosterone and Estradiol supplementation was necessary to fully restore sexual function in castrated mice with no aromatase[11].
- E2 has been shown to maintain the excitability of bulbospongiosus muscle activity in castrated rats, and is important in pelvic floor function[8].

This knowledge establishes a surface-level understanding to substantiate the assumption that **direct or indirect effects of severe Estradiol reduction are behind the emergence of PAMD.** However, questions regarding the persistence of symptoms despite the return of serum Estradiol levels to physiological ranges as well as direct links of estradiol to the symptomatology remain, and will be subsequently addressed. Before that, let us establish that there is enough similarity between syndromes to allow the possibility of an identical cause.

Connecting the dots between Syndromes

In order to examine the connection between syndromes, we will begin with the more generic assumptions and move towards specificity.

The law of simplicity, Occam's razor dictates that entities should not be needlessly multiplied. If **presentation**, **symptomatology**, **diagnosis, prognosis** and **treatment** are identical, it is far more likely that the conditions themselves are actually identical, than it is they are not. This serves as an indicator to carefully examine the common grounds, and can lead towards understanding the underlying mechanisms. A closer look at these characteristics is due:

- **Presentation**

  All 4 Syndromes present in a nigh-identical manner. They are characterised by dysfunctions that may appear to some degree while undergoing treatment of a particular medication, but differentiate and truly present **after cessation of treatment**. They all **appear abruptly**, with full symptomatology manifesting quickly after initial symptom appearance. Sufferers report taking **various dosages** of the medications among all 4 conditions. At the same time, **the majority of people who take any of the 4 medications will not report manifesting the same syndrome**, even on objectively equal doses to those taken by people who will. This holds true with PAMD as well, as AIs are very often abused by AAS users to equally severe degrees in preparation for bodybuilding contests or other competitions with no reports of permanent aftereffects .

Also by breast cancer patients, among others, who use these medications regularly for years with side effects that resolve after discontinuation. As a result, **the actual existence of all 4 syndromes is always under scrutiny and doubt**.

- **Symptomatology**

  As already explained, symptomatology is essentially identical among all Syndromes. **Major symptoms are identical**, with minor symptoms **often overlapping between groups** but showing variation between individuals of any group. An interesting observation is the appearance of genital insensitivity across all 4 syndromes. Genital insensitivity is perhaps of special importance, as it is an otherwise rare symptom that only appears after rare neurological conditions, infectious disease or injury.

- **Prognosis**

  All Syndromes are reported to **remain equally severe with little to no improvement over time,** although recovery does vary between patients. In general, once the syndrome appears it will persist for a significant amount of time (months or years), even among the cases that end up recovering. The commonality of full recovery is unsettled due to lack of sufficient reports.

- **Diagnosis**

  Sufferers of all 4 groups have reported psychiatric, psychologic, endocrinological, urological, cardiovascular, immunological and neurological examinations that failed to consistently lead to diagnostic criteria of any known condition. In general, sufferers appear to be healthy, blood test markers are normal and positive results that would point to a certain direction have so far been inconsistent among them. PAMD does have fewer reports in this regard due to being a lot rarer, but follows the same trend, with multiple sufferers reporting regular blood tests and countless doctor visits to no avail.

- **Treatment**

  A long list of treatments, ranging from supplements and alternative medicine to further psychiatric medications and hormone replacement therapy have been attempted with equally inconsistent results. However, reports of a few particular treatments that have lead to recovery across the syndromes do exist. In this thread, there are at least 30 accounts that reported significantly healing or even fully curing their PSSD via methods all of which severely increase androgen levels, and reporting lasting recovery even after discontinuation of exogenous supplementation. This prompted the speculation that androgen deficiency plays a part in PSSD. As a result, many sufferers tried Testosterone Replacement Therapy. However, those who tried TRT report little to no improvement. This holds true across communities, with PFS sufferers reporting similar resolution with some androgen-increasing methods, but attempting DHT supplementation and TRT to the same disappointing effect.

The differentiation between the failed and successful strategies is easy to see with some basic knowledge of how both sex hormones, androgens and estrogens work. The successful ones, consisted either of:

a) Supraphysiological doses of Testosterone or supplementation with extremely potent androgens such as Mesterolone(Proviron) or DHT.
b) Extensive clomid (clomiphene citrate) use. Usually for a period longer than a month, with relatively high and frequent dosing (25 or 50mg every day).
c) A combination of both, beginning with high T injections and ending with clomid use, something which is akin to a “bodybuilder steroid cycle” which consists of large doses of anabolics, followed by what is called Post-Cycle Therapy (PCT) to reset endogenous hormone production which the exogenous anabolics shut down.
d) With lesser effect, Human Chorionic Gonadotropin(HCG) supplementation.

Despite their similarly androgenic effects, these methods are not similar to TRT. The amount of Testosterone administered in a single AAS-type dose is 4 or 5 times the amount of the highest TRT-type dose. In other words, the androgen doses that proved most effective produced an abrupt and severe increase in androgen levels. The second differentiating point concerns E2 levels. TRT protocols administer physiological doses of Testosterone and thus keep E2 in controlled physiological levels, and sometimes further reduce them with AI use (which is quickly suggested by TRT clinics at any hint of high E2 readings), whereas the methods detailed above **all induce significant Androgen and Estradiol elevation.** To explain further:

a) Increases in Testosterone produce increases in aromatisation, as excess testosterone is present for aromatisation. Larger increases exacerbate the effect. In supraphysiological ranges, this effect is further potentiated, as a limiting factor in T and E availability is the Sex Hormone-Binding Globulin(SHBG) which binds to Testosterone, DHT and Estrogen and does not allow them to activate androgen or estrogen receptors. SHBG levels however do not rise proportionally with sex hormones when exogenous testosterone is administered, allowing free levels of both sex hormones to be exponentially increased with supraphysiological doses.

b) Clomiphene(Clomid) works by blocking the estrogen receptor, which regulates HPA activity through the HPA negative feedback loop[12]. When the estrogen receptor is blocked, HPA activity is upregulated significantly. This increases Testosterone production, and Estradiol levels as a byproduct. Clomid consists of two stereoisomers, Enclomiphene and Zuclomifene. Shortly After discontinuation of clomid, testosterone levels return to baseline but the estrogenic effect of clomid gains traction - as zuclomifene remains in the system long after enclomiphene has been cleared out. Zuclomifene is an estrogen agonist, synergising with endogenously produced Estradiol to further increase estrogen receptor activation. This aligns with reports that resolution of symptoms did not appear **during** clomid administration, but rather **after** cessation of clomid, further linking their recovery to a significant increase in androgens, followed by a return to androgen baseline and an increase in estrogens, before eventually returning to a steadily functioning endogenous hormone production.

c) A combination of high T doses and subsequent Clomid administration is a combination of the above two effects, thereby also resulting in increased androgens followed by increased estrogens.

d) HCG monotherapy stimulates HPA activity, therefore increasing both testosterone and subsequently estradiol. It is reported as less effective than the other two medications and usually only results in minor, temporary alleviation. HCG by itself does not produce supraphysiological androgen increases nor a potent estrogenic effect, and its reportedly low and transient effectiveness makes sense, as it does not follow any of the two patterns described above.

It should be noted that no use of AI has been reported in these methods. The last noteworthy characteristic is the **acute** nature of both androgen and E2 increases in the successful reports and the fact that recovery has been reported to persist long after treatment discontinuation. The importance of the acute nature of the increases will be discussed further.

The realisation that Estradiol has been a common factor in the resolution of all syndromes provides another link between them. Perhaps the most important observation of similarity thus far has been that sufferers of all four share the display of perfectly healthy individuals. Thus, it is not necessarily an issue of complex disease, but first and foremost an issue of complex diagnosis. Until this day, even if we were to assume a common cause, the complexity of the medications and subpar understanding surrounding the systems they affect could still allow for a complex and obscure mechanism of action that can cause all three. But the addition of PAMD, which comes with much clearer links between cause and effect changes the setting. Again, parsimony dictates that having 4 separate disorders all of which affect the sufferer in a near identical way, yet are all caused by different, highly obscure and specific mechanisms none of which produce readily measurable effects, is highly unlikely. If we can verify the addition of a possible common treatment to these commonalities it would make the probability of their distinction near impossible.

At this point, two important observations aid in connecting the syndromes:

Observation 1:

Major symptomatology in these syndromes is too generic to necessarily lead to any overtly specific aetiology, but some of the often-reported, but differing across individuals, minor symptoms of all 4 are all directly related to either estradiol deficiency or an androgenic environment. For example, reports include:

- Dry, irritated skin and other skin conditions. Estrogen is vital in maintaining the health, elasticity, moisture and thickness of skin[13,14,15].
- Joint pain. The function of estrogen in maintaining joint and bone health is well-known[16].
- Changes in Smell/Taste can be explained by estrogen deprivation, and Estradiol supplementation stimulates increased olfactory sensitivity[17,18,19].
- Vision problems. Variations in estrogen levels correlates to changes in vision in women[20], and breast cancer patients undergoing estrogen deprivation therapy exhibit retinopathy[21].
- Pelvic floor dysfunction in women is an area where estrogen supplementation plays a significant role in symptom alleviation, including the reduction of recurrent UTIs[22]. Several studies have found shared pathogenetic mechanisms between pelvic pain,

bacterial prostatitis and IC, which have been linked to estrogen receptor deregulation and pelvic floor dysfunctions in men are known to respond to phytoestrogens like quercetin[23,24].

• Decreased vaginal lubrication. Considered a hallmark symptom of menopause, it has already been linked to reduction in estrogen levels, and commonly treated with topical estrogen creams[25,26].

• Apathy and depression. Estrogen works to stimulate and inhibit the HPA-mediated adrenal response[27], and its effects in relation to anxiety and depression are a significant topic in understanding these pathologies[28,29].

• Anhedonia. Inability to feel pleasure and reward, even from activities which would induce them in the past, often leads sufferers to speculating a relation to dopaminergic activity in the brain. Dopamine agonists such as amphetamines are reported to have reduced effects on PSSD patients. Estrogen has a key role in dopamine regulation, affecting transporters and receptors among other mechanisms[30,31,32]. These include the intriguing observations that apoptosis of dopaminergic neurons occurs spontaneously in the adult male, not female, hypothalamus of mice deficient in aromatase, who lack the ability to locally synthesise estradiol in brain areas. Estradiol, and the differences in its concentrations among genders are key players in major discussions regarding the development and treatment of neurologic and psychiatric diseases like Parkinson's.

• Difficulty falling asleep and restless sleep. Sleep difficulties are presented in estrogen deprived patients, and estrogen supplementation successfully treats sleep quality in menopause[150,151,152,153].

• Memory and cognition. Estradiol modulates cognitive functions, memory consolidation and synaptic health. Direct fluctuations in estradiol correlate to fluctuations in learning and memory capacity. Reduction in estradiol levels during menopause are thought to exacerbate aging declines in cognitive functions[146,147].

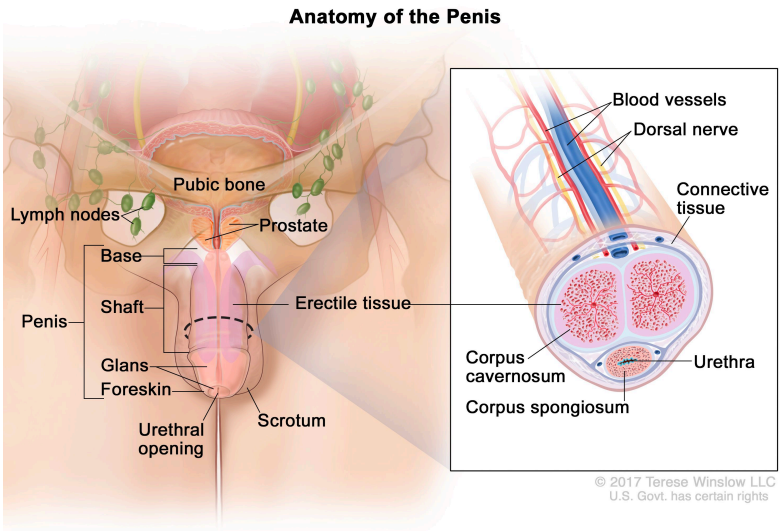
• Scalp hair-loss or thinning. A quick search for "hair loss" on the PSSD subreddit comes up with a long list of results. Search terms as "hair thinning", "balding", further increase the list of reports after SSRI discontinuation. In PFS, hair loss preceded treatment and thus its resumption is expected after discontinuation, but nonetheless indicates an androgenic environment. In a severe case of PAMD, hair loss was also reported, despite no prior indication or genetic predisposition. Dihydrotestosterone (DHT) is known to affect hair follicles and attenuate male-pattern hair loss where genetic predisposition is present, but estrogens are equally important. Indirectly, as the majority of estradiol in males is synthesised by aromatisation of Testosterone, any decreases in aromatase activity lead to higher levels of DHT and directly, as estradiol exerts significant effects on the hair cycle[33,34,35].

• Temperature changes, fatigue. E2 modulates a number of hypothalamic-regulated autonomic functions, most notably energy homeostasis and temperature[36].

• Muscle loss and weakness. Although Testosterone exhibits the main role in anabolism between sex hormones, Estradiol is vital for preventing muscle loss and weakness through inhibiting apoptotic mechanisms[37,38,39,40].

• Lower libido has already been correlated to low E2 levels in men[9,41,103] and change in estradiol level was the best predictor of sexual desire when estradiol administration was compared to DHT and Testosterone administration in hypogonadal men[42]. In an aromatase-deficient man who reported normal sexual function, administration of estradiol did not affect sexual orientation but produced an increase of libido, frequency of sexual intercourse, masturbation and erotic fantasies - and a reduction in Beck Depression Inventory and Spielberger Trait Anxiety Inventory scores[43]. Furthermore, administration of estradiol in castrated male rats provoked an acute increase in sexual behaviour, where Testosterone administration displays a latency before producing similar effects, suggesting that aromatisation, and thus estradiol is directly necessary for said increases[148]. Finally, in men undergoing testosterone supplementation therapy, low libido was correlated with low but not high estrogen levels[149].

• **Flaccid glans during erection** and **genital insensitivity**: The crucial role of testosterone in facilitating erections is well known. It is certain that sufficient levels of Testosterone are necessary for maintaining smooth muscle tissue in the penis, preventing atrophy and formation of connective tissue. The role of estrogen is not yet clear, and it is thus neglected when treating erectile dysfunction. However, estrogen receptors in the human penis are detected in large concentrations in the urethral epithelia, Corpus cavernosum and corpus spongiosum[44,45]. Moreover, ERs and aromatase are present in the blood vessel lining and walls of human penile tissues, suggesting a role of estrogen influence in vasculature[46]. Further estrogenic effect on penile vasculature is suggested by E2 facilitation of NO production by increased eNOS expression and level of activation, and also by a regulatory role on Vascular endothelial growth factor(VEGF) expression and modulation of its effects[47]. Perhaps more importantly, ERs and aromatase activity are also localised in the penile nerves. Quoting



Mowa et al., 2006:

- "ER and aromatase in the rat and human are localized to the penile nerves (Jesmin et al., 2002, 2004; Crescioli et al., 2003). The presence of ER-α and aromatase in the rat sensory corpuscle of glans penis, containing the highest concentration of sensory nerve fibers vital for sexual sensation (Kandel et al., 2001), is interesting and intriguing, particularly because both ERα and ERß have been identified in neural circuits involving central neurons, autonomic and sensory ganglionic neurons, and spinal cord neurons in areas that have connections with the male reproductive systems (Taleghany et al., 1999; Burke et al., 2000; Murphy and Hoffman, 2001). Estrogen may likely be important

in the survival and vitality of sensory corpuscles and, consequently, on sexual sensation. It is also important to note that the main efferent parasympathetic pathway supplies vasodilating innervation to the cavernosus bodies, whereas the main sympathetic pathway supplies mostly the vasoconstriction innervation, thus chiefly mediates detumescence (Kandel et al., 2001). Finally, it is interesting to note that levels of ER, together with AR and progesterone receptor (PR) are down-regulated in the penile crura of aging rats and are associated with aging-related erectile dysfunction (Shirai et al., 2003)."

A noteworthy observation regarding the estrogenic effect on male erectile function comes from the reports of steroid users. Reports agree, though too high estrogen levels lead to ED, they do not lead to loss of libido or genital numbness, in fact usually demonstrating increased libido and sensitivity. On the other hand, when estrogen levels fall too low, sexual dysfunction of the same magnitude as the four syndromes is reported. Libido is severely impaired, even transient **asexuality** and apathy towards the opposite gender is reported, loss of penile sensitivity occurs making erections impossible, and orgasms are muted[48]. The type of ED reported when E2 levels are too ***high*** is also worth close attention. Reportedly, erections can be produced but not maintained, or are less rigid[48]. This points to vascular over permeability, known as Venous leakage, which is in fact tied to high estrogen levels[49]. This link however also serves as evidence of estrogenic effects on facilitating erectile blood flow and the necessary environment for an erection. Insufficient vascular permeability may explain the pain felt during erections in syndrome patients, as blood flow is restricted and tension is increased(also leading to a flaccid glans). These effects make the case for a specific T/E ratio which maintains E levels inside a yet undetermined range that allows for sensitivity, libido, and a proper vascular environment - but not high enough to lead to ED through venous leakage. This is further substantiated by Chen et al., 2020 on the correlation of different levels of E2 with sexual dysfunction in men, where a progressively increasing graded-distribution of estradiol values from Delayed Ejaculation to Premature Ejaculation and Erectile Dysfunction was found, with delayed ejaculation at low levels perhaps signifying a decrease in penile sensitivity and arousal.

These observations coupled with the specificity of this symptom, and with its common appearance across syndromes contradicting its otherwise rare nature, make it particularly important. The fact that patients of all syndromes can still exhibit forced erections, but usually experience pain, flaccid glans and insensitivity during erection, already point to vascular and nerve issues (and not smooth muscle issues, to which T is linked), specifically in and around the glans. Connecting estrogen to the vascularity *and* nerves of the specifically problematic areas in the syndromes is certainly not a coincidence. It serves to also remember that penile skin in PFS patients was found to have smooth muscle and nerve density similar to controls, but **a 2-fold higher ratio AR positive stromal cells % to serum testosterone concentrations**[50], signifying androgen overactivity.

- The ineffectiveness of PDE-5 inhibitors which usually only produce artificial erections and do not aid libido or sensitivity in syndrome patients is consistent with our assumptions and explained by their pro-androgenic and aromatase-inhibiting, anti-estrogenic effects[51,52,23].
- PSSD sufferers often report immune system-related symptoms and increased immune response markers. Sex hormones play an important role in the regulation of the immune system. Androgens and progesterone are immunosuppressive whereas estrogen generally exhibits immunostimulatory effects. Particularly, Estrogen receptors are widely expressed in immune cells[54] and estrogen modulates infection response and severity, recovery and long-term immunity after infection, and exhibits anti-inflammatory properties[55]. Complex interactions of hormones and environmental factors in genetically susceptible individuals lead to deregulation of the immune response, leading to immune-mediated diseases including autoimmune disease[56,55].

Before moving on, it should be pointed out that many of the symptoms described above, such as:

1. Thinning hair / hair loss
2. Dry skin
3. Joint and muscle pain
4. Muscle weakness
5. Changes in smell/taste
6. Vision problems
7. Pelvic floor dysfunction and genitourinary symptoms (Interstitial cystitis)
8. Decreased vaginal lubrication and clitoral/vaginal sensation
9. Depression
10. Apathy
11. Anhedonia
12. Temperature Changes
13. Reduced libido

are all described as symptoms of menopause, where the predominant factor is reduction in estrogen levels[57,58]. At the same time, they are listed as side-effects of Estrogen deprivation therapy in cancer patients, either through aromatase inhibition or estrogen blockers[nhs.uk]. (AI side effects are actually characterised as “symptoms of menopause” by cancer.org) and finally are also reported as low E2 symptoms by AAS users[48]. As expected, equally similar reports are found at any gynaecological cancer forum in threads pertaining to the use of AIs. The only difference between them and the syndromes is their transient nature (resolution upon discontinuation) and severity. Depersonalisation and loss of self are also reported by AAS users as Low E symptoms and as severe AI side effects in cancer forums(figure 2)

https://community.breastcancer.org/forum/67/topics/826766

> I am so miserable. Have been for almost 2 years. I've done it all....acupuncture, mediation, hypnosis, therapy, herbs, etc etc... I havnt slept in over 2 years. Depressed. Apathetic. at times suicidal.

https://community.breastcancer.org/forum/78/topics/851224

> I think I am on the edge of depression. I am not sad or feel pity, I just have feelings of not caring about anything anymore. I don't care how I look, I don't care if I see my friends, I don't care to do any of my favorite activities. The things I am doing now is like just going through the motions because I don't want anyone to know what I don't feel. My short term memory is getting terrible.

https://community.breastcancer.org/forum/78/topics/755969?page=221#post_3316225

> I took Arimidex for 3 months with progressively worsening side effects. I took a self-induced "break" 2 weeks prior to seeing my onc without significant change. My third week OFF of Arimidex and I am starting to feel human again! I actually 'jogged' up the stairs for the first time in months..., I went shopping after work without feeling as if I would fall asleep behind the wheel on my way home.., it's small stuff but reassured me that I wasn't crazy!

> I feel for all of you! Pains and aches are no picnic and I am no stranger to them! Unfortunately what is bothering me now even more, is my uncontrollable appetite, memory loss and a general feeling of apathy, and let's NOT forget my constant feeling of living in the NORTH POLE!!! Hello, I could use an hot flash once in a while.....
> I felt more alive and positive after I found out my DX than I do now....Now I feel like I want to just crawl under a rock and stay there! I know it has to be the Arimidex because all these problems started recently.

https://community.breastcancer.org/forum/78/topics/754655

> Started this poison May 6. Will not take it again. I was on tamoxifen for 15 mos. and had horrible hip pain and hot flashed about 40 a day. So went to arimidex. The depression and flat affect has made me totally uselss a zombie. Onco is sending me for every test under the sun...but this severe depression did not start until I took arimidex. I have a 18 yr old son and 14 yr old with cerebal palsy. I actually looked at my Xanax bottle today and contemplated taking them all.. Very scared was never depressed or suicidal. I am on leave of absense from work just totally unable to function on this drug. Found my milk in the kitchen cabinet. Is anyone else feeling this was?? I can take all the joint pain it causes. I cannot let this rob my mind and sanity. thank you all for listening.

Figure 2. Reports of symptom similarity in breast cancer patients undergoing AI treatment.

Observation 2:

Similarities in the hormonal effects of the medications that precede PSSD, PFS and PRSD:

- Finasteride is a 5a-reductase inhibitor. Its mechanism of action is to inhibit the formation of dihydrotestosterone (DHT) from Testosterone by inhibiting the necessary catalyst to the process. It has been shown to achieve reductions upwards of 70% in DHT, which is linked to male-pattern baldness[61].
- The precise pharmacological mechanism of action of **isotretinoin** is not known[62]. Isotretinoin treatment has been found to impact DHT and serum 5 alpha reduced androgens. It is theorised that its role in decreasing DHT is part of its efficacy in reducing acne, as sebum production is heavily modulated by androgens[63,64,65].
- The disruptive effects of SSRIs in the endocrine systems of humans have been suggested both by the commonality of sexual dysfunction in patients undergoing

treatment and by studies on these effects. For example, SSRI use has been associated with menstrual cycle disruptions and breast enlargement in women and similar effects have been found in mice[66,67,68]. Further studies are necessary to determine the exact mechanisms through which these effects are produced. Fluoxetine, one of the most prominent medications in PSSD, has been demonstrated to interact variably with estradiol concentrations and estrogen receptors[69,70,71]. An interesting study on 6 of the most commonly used SSRIs in vitro, showed confirmed the potential of all 6 for endocrine disruption by interfering with steroidogenesis and also that although different structurally, all 6 substances resulted in an increase in estrogenic effects and changes of the androgen to estrogen ratios[72].In addition, estrogen supports supports serotonin levels and affects the amount of 5-HT receptors in the brain, modulating sexual inhibition or facilitation depending on receptor subtype[73,74,75,76,77]. Serotonin and estrogen share complex interactions that regulate these effects[78,80].

The hormonal effects of the above medications have not been sufficiently studied to establish direct and certain conclusions. The lack of evidence is especially apparent where antidepressants are concerned. Nevertheless, there are strong suggestions as to the hormonal environments that result with their administration, which is further potentiated by close resemblance across all characteristics of the resulting syndromes and its relation to another setting where the aetiology is known to be estradiol deprivation. That is, the setting of gynaecological cancers, where use of Aromatase Inhibitors, ovariectomy and other medications, achieves near eradication of Estrogen levels, resulting in the exact same symptomatology found in PSSD, PFS, PRSD and PAMD across patients and varying by severity and duration of treatment. Of special importance is the symptom of **genital insensitivity,** which is not commonly found in conditions that do not involve physical injury, severe neuropathy or infection, yet exists across these settings, including the setting of transient E2 elimination in AAS users[48]. Considering the above, it is not unreasonable to speculate that the root cause of all 4 syndromes is an estrogen-related **dysregulation**, the crucial role of which we have already established and linked to all the common symptoms. That questions that do remain are as follows:

- How the medications lead to chronically low estrogen activation.
- Why the symptoms appear after discontinuation.
- Why all patients display normal, physiological levels estrogen in blood tests.
- What prevents recovery.
- How the common treatments fit the supposed root cause.
- What prevents contraceptive use or HRT in treating PSSD symptoms in women

An attempt to answer these questions with answers backed by the scientific literature will follow. Though the existence and function of the mechanisms that will be detailed in the answers is well-established, there is little to no **direct** evidence linking them to the syndrome. The nature of the conclusions is speculative by default, and is only

meant to show that the proposed cause is indeed possible instead of determining exact mechanisms.

Diagnosis and syndrome provocation

The side-effects of taking these medications are differentiated from the resulting syndrome after their discontinuation. One is not considered to have PSSD, for example, *while* undergoing SSRI therapy. In fact, the short period directly after discontinuing the medication is also not necessarily associated with PSSD. PSSD is diagnosed when symptoms persist at least 3 months after cessation of the medications[79]. The same applies for the other syndromes as well. To what degree the sexual side effects that occur during treatment are related to those that occur after, may or may not vary with each medication, but is nonetheless irrelevant to this theory.

The fact that full symptomatology appears and worsens only after discontinuing the medication is an important observation. It could point to a prolonged withdrawal, rebound effect, or epigenetic changes induced by the medication. As argued in the introduction, considering the reports of recovery, windows of improvement, and variability in treatment protocols that resulted in the syndromes, a long-term toxicity exposure-induced permanent neurological damage is unlikely. Instead there is a simpler answer that shares common ground with all medications, and fits what has been established up to this point:

Medically induced chronic estrogen receptor dysregulation. In other words, **acquired estrogen resistance.**

Here is how this can be explained in the setting of all medications:

- Finasteride and Isotretinoin, by severely reducing DHT and indirectly increasing Estrogen levels, induce a l**ong-term significantly pro-estrogenic environment** and severely **decrease androgens** during treatment. SSRIs likely produce a similar pro-estrogenic environment through interactions with mechanisms described above.
- All medications are usually taken for significant periods of time, and their effects of each medication are long-lasting due to a long half-life in the case of isotretinoin(22 hours[81]), half-life and metabolite half-life in the case of fluoxetine(1-4 days and 7-15 days respectively[82]), escitalopram(27-33 hours)[83], etc. and due to effects from which recovery takes time in the case of Finasteride(6-8 hour half-life but significant DHT suppression from a single dose lasting up to 4 days[84] and 14 days to return to normal DHT levels[85]).

Variations in hormonal levels provoke adaptations in expression and activity of Estrogen and Androgen Receptors[86,87,88,89,90,91]. Estrogen deprivation has been shown to lead to ER oversensitisation, whereas constant activation of ERs to desensitisation[88,90]. The same process occurs with ARs.

If we consider the environment created by the medications concerned, it is not unreasonable to assume they may produce similar effects. Through effectively decreasing DHT, the pro-estrogenic environment these medications create, promotes exactly these two effects. As the body is starved of DHT, ARs upregulate in response. At the same time, ER activation is significantly increased as a result of the increased production of Estradiol during treatment (due to higher Testosterone availability by reduced 5a reduction to DHT) - eventually leading to ER downregulation.

Then, the medications are ceased. At this point, the long half-life of the medications, as well as the restoration of DHT levels through 5a-reduction being a slow and time-consuming process, mean a gradual and steady return to normal levels. There is no abrupt rebound that would provoke another adaptive response to reverse initial adaptations. Instead, the levels return slowly, and the adapted hormonal environment now influences the actions and distribution of the rebounding sex hormones. Eventually this results in a chronic state of downregulated ERs but pre-treatment levels of circulating E2 - and upregulated ARs but pre-treatment levels of DHT, thus increased androgen presence and estrogen insufficiency.

In the case of SSRIs, this specific deduction is harder to make given the insufficiency of evidence regarding endocrine activity. However, as previously mentioned, the relation of SSRIs to Estrogen, its receptors, estrogenic effects as well as the interactions and synergies between estrogen and serotonin are evident. Thus, a similar scenario of a pro-estrogenic environment by increasing estrogenic activity and reducing ER expression, or more plainly a decrease in ER expression alone could lead to similar adaptations, which are not restored after discontinuation for the same reasons of long half-life and slow, marginal restoration of hormonal activity to baseline.

To further connect the abrupt disruption and slow rebound to the emergence of the syndromes, let us consider PAMD for a moment. As explained, PAMD is alleviated by increasing Estradiol levels. However, where the medications of the 3 other syndromes create a pro-estrogenic environment, Aromatase Inhibitors create a pro-androgenic environment and estradiol starvation. This contradicts the resulting estrogen-resistant environment. It would be expected that rebounding from estrogen deprivation would lead to estradiol overabundance and thus PAMD should be a case of too high estrogen levels.

However, the chronic state of PAMD does not appear directly after ingestion of AIs. Instead, it appears after a sequence of events that take place over a period of days, and the starting point of which is an initial estradiol starvation.

To accurately describe the series of events that precede PAMD:

1. **After overuse of AIs, a state of severe Low E2 symptoms appears.**
2. **This prompts the user to immediately discontinue all AI use.**
3. **Low E2 symptoms subside, but a rapid increase in E2 levels follows.**

   Due to prior AI use and due to the latest abrupt deprivation of estrogen, the body is primed for an overcompensation in estrogen production. Various adaptations take place to facilitate this rapid rebound:

• Estrogen receptors are upregulated.

• Secretion of aromatase is upregulated.

• SHBG is decreased, binding less Estradiol and Testosterone, which can now be aromatised further[92].

• The absence of estradiol prevents inhibition of the HPGA and prompts the secretion of large amounts of GnRH to facilitate eventual Estradiol production.

These adaptations are an effort of the body to adapt to the abrupt E2 deprivation.

4. **The compensatory response leads to a transient state of *high* E2.**

   As the AI is cleared from the body and discontinued, nothing remains to necessitate the presence of these adaptations. As a result the increases overcompensate, quickly leading to the immensely pro-estrogenic environment that precedes the appearance of PAMD. Users at this point report feeling bloated, increased nipple sensitivity and emotion intensity, all symptoms of this compensatory fluctuation.

5. **With a delay of a few days, the above symptoms subside.**

   It is during this period that reverse adaptations are taking place. The adaptations are prompted by the abrupt changes in hormone levels, not the aromatase inhibitor itself. It is only reasonable to expect another adaptive response to this pro-estrogen environment, considering the cascade of effects that took part in the initial adaptive response and the magnitude of that response itself. The second response consists of the following effects, all mediated by the abrupt and prolonged increase in estrogenic activation.

• An increase in SHBG levels

• A prolonged inhibition of the HPGA, until estrogen activity declines enough to restart normal function.

• Downregulation of estrogen receptor activity.

These adaptations lead to the hormonal environment that constitutes the symptomatology of PAMD.

6. **The chronic state of PAMD appears, and no further changes follow.**

   Precisely because this resulting environment arrives after slow and gradual recovery, now free from further abrupt disruptions, the adaptations are mostly maintained, and the new baseline of hormonal activity produces PAMD. Essentially, corrective adaptations for a significantly increased Estradiol presence, remain after estradiol presence returns to normal.

   The above events are usually described to happen within a period of around 10 days, with variations between reports. Only a situation similar to the one described above can explain how a medication that induces severe estrogen deprivation results in

chronically low estrogen symptoms after discontinuation. This substantiates the argument for the necessity of abrupt hormonal imbalances and a pro-estrogenic environment preceding all syndromes.

The mechanisms behind the adaptations

Similar reorganisation is known to occur after changes in the hormonal environment through other pathways. The removal of the gonads, perinatal exposure to sex hormones and the hormonal increases during puberty, all cause an abruptly altered hormonal environment, which subsequently leads to changes in receptor expression[84,86,87]. For example, pubertal emergence of sexual behaviour is induced by increased gonadal production and accompanied by synaptic reorganisation of the amygdala. This reorganisation of a key network involved in the expression of sexual behaviour, is mediated by androgens[93]. It is therefore not unreasonable to assume that a disruption of similar degree by other mechanisms may induce severe changes in receptor expression and activity. In fact, the effects of Finasteride administration have already been compared to gonadectomy or old age, and persistencies in alterations of the hormonal environment have been demonstrated[94,95,96].

Whether these changes may occur exclusively by increases and decreases in AR and ER expressions as opposed to degree of transcriptional activity or by a combination of both, may depend on the mechanisms of action of each particular medication and accompanied signalling. As previously discussed, for example, fluoxetine has shown a distinct effect on ER expression. These differentiations along with genetic factors may explain the minor differences between presentations, such as differences in dosing and duration of treatment prior to syndrome appearance.

Findings have demonstrated dissimilar regulatory profiles of ER and AR mRNA, signifying that changes in androgenic and estrogenic activity do not necessarily correlate or influence one another directly[87]. Estrogen but not androgen has been shown to reverse castration effects on ER mRNA, demonstrating a greater specificity of the autoregulatory mechanism for the ER gene[87]. Where AR mRNA is concerned, besides autologous regulation by androgens[87], estrogen appears to display regulatory properties on AR expression and activity. Studies have demonstrated estrogen supplementation is followed by increased AR binding[97] and nuclear AR occupancy[98], which may be accompanied by increases in AR mRNA[87]. Thus, significant reductions in estrogenic activity may lead to reduced androgenic activity despite normal androgen hormone presence. These complex interactions and the vital importance of estrogenic activity are demonstrated in castrated rats, where treatment with a non-aromatisable androgen, DHT, is incapable of fully restoring masculine reproductive behaviours unless co-administered with estrogen[99,100,101], also in hypogonadal men where administration of both hormones leads to the best response in restoration of sexual activities[102,103].

In the case of the 4 syndromes, where profound decreases in estrogenic activity are suggested, the suggestion of estrogen-mediated regulation of androgen activity is

consistent with reports of lessened androgenic effects and lessened response to androgens and TRT protocols. Whether androgen activity is overabundant or insufficient in patients of the syndromes is uncertain, considering the reports of reduced response to androgens but findings of elevated AR mRNA in penile tissue of PFS patients. A lack of correlation between AR mRNA and AR binding[87] may point to underactivity despite presence of increased AR mRNA. Underactivity may also explain why AR mRNA remains increased with return of normal hormonal levels and is not autologously regulated to baseline. Nevertheless, restoration of normal sexual function will necessitate return of AR and ER activity to baseline, and not knowing the answer to the above question is of little importance as the ways we would go about correcting the levels of said activity are the same whether it is too high or too low.

Finally, differentiation in actions between ER subtypes may point to specific aetiology. ERα subtype is shown as the key factor in the regulation of transcriptional activity of estrogens on reproductive behavior and physiology as demonstrated by studies on mice with ERα knock-out[104,105]. ERβ does not share this characteristic[106,107], but appears to be solely responsible for the rapid regulation of sexual behavior[108, 109]. Considering the variety of symptoms caused by the 4 syndromes concerns both types of activity, it is likely that both subtypes are affected - though ERβ dysregulation may be more important where sexual inhibition is concerned and ERα in genital sensitivity.

Serum/Local estrogen presence - The importance of local ER activity

The differentiation between tissue-specific and peripheral estradiol levels may explain dysregulation in spite of appearance of regular blood tests. Comparison of serum Testosterone, Estradiol and Progesterone hormone levels in plasma to cerebrospinal fluid in men with no neurological disorders showed very weak correlations between the two, signifying possible discrepancies in neurosteroid activity compared to serum[110]. Though the results are not conclusive, it is possible that neurosteroid imbalances do not show in plasma.

A point of significant importance is the reliance on tissue-specific estrogen presence to facilitate estrogen-mediated effects independently of peripheral levels. This was demonstrated in studies on the effects of local biosynthesis of estrogens. Where total Aromatase knock-out(tArKO) mice exhibited complete absence of sexual behavior, brain-specific Aromatase knock-out(bArKO) mice exhibited a 50% decrease in the number of mounts and intromission[101], demonstrating that aromatase presence and local E2 synthesis in the brain is significant for facilitation of sexual behavior and other estrogenic effects[111]. Intact bArKO mice demonstrated strikingly elevated levels of Testosterone, yet reductions in sexual activity that T administration could not ameliorate. In castrated bArKO mice, Testosterone treatment did not fully restore sexual behavior deficiencies. Addition of E2 to T treatment was necessary for restoration of normal sexual activity[101]. As already noted, administration of E2 in an aromatase-deficient man also lead to increase in sexual activity[43], and concomitant administration of both T and E2 was

necessary to improve sexual function in another man with aromatase deficiency and hypogonadism[102]. This data on brain specific actions of aromatase suggest that although testicular aromatase plays a dominant role in male sexual behavior, brain aromatase specifically contributes to regulating the initiation and frequency of sexual activity[101,111].

These studies are relevant because aromatase inhibition can affect brain-specific estrogenic effects more potently than other methods that reduce peripheral levels. The brain relies in local production of Testosterone and Estradiol, both directly and through aromatisation, to potentiate rapid local increases in estradiol levels, independently from serum, which are necessary for estrogenic effects that depend specifically on said increases to modulate sexual arousal and other important functions in both males and females[112,113,114,115]. Aromatase inhibitors effectively cross the blood-brain barrier in a dose dependant manner. The inhibition of aromatase thus impairs these mechanisms where other means of estrogen reduction may not, and displays the disconnect between serum levels and brain-specific estrogenic activity, which serves a potent explanation for symptomatology across the 3 syndromes, and another link between them and PAMD.

Estrogen resistance further explains the normal, high normal, and sometimes above range serum levels of Estradiol in patients across the syndromes. In two distinct case studies(one male, one female) of genetic estrogen resistance and its presentation, both patients presented with significantly elevated levels of serum estradiol[116,117]. In the male, a compensatory increase in aromatase activity in response to estrogen resistance, which could account for the normal levels of Testosterone despite increased secretion of luteinising hormone was suggested. In the female, serum estradiol levels were found to be 10 times above the physiological range. Another consideration is that decreased receptor count, binding and transcriptional activity in tissues likely results in higher hormonal levels in serum, as more of the hormone remains unbound.

The syndromes should not be further compared to the aforementioned case studies due to the obvious significant distinctions between genetic mutations that have been present since birth and acquired conditions, but it is safe to conclude that reduced ER activity may present normal or above range serum E2 levels and otherwise regular hormonal profiles. It is important to keep in mind the difference in severity of estrogen resistance between the syndromes and these two case studies, as the effects on serum levels will certainly be less pronounced as a result and will therefore not necessarily show elevation above defined ranges, when accounting for the wide range margins provided for these hormones.

Inhibition of recovery

An important factor in the inability of the body to recover efficiently, is the negative feedback loop that controls the circulating level of sex hormones. The HPGA is mainly regulated through Estrogen, with androgen and progestins playing secondary roles that appear to be estrogen-dependant[12,118]. When estrogen receptor activation in the hypothalamus is insufficient, inhibition of the HPGA is lifted and secretion of GnRH by the hypothalamus kickstarts the eventual production of sex hormones, which will then lead to increased Estradiol, ER binding and activation and finally inhibition of the HPGA. If the specific mechanisms and receptors that modulate this process in the HPGA are unaffected by the medications, thereby allowing for unaffected hormonal production, Estradiol could never reach sufficient levels to overcompensate for the downregulation of ERs in other areas of the brain and body - as its increase directly inhibits its further production. If those mechanisms *are* affected, and we assume that HPGA inhibition now also requires higher estradiol concentrations due to ER resistance, then higher hormonal production will be induced, but is still unlikely to prompt recovery, as inhibition will eventually occur at a minimal point, insufficient to correct for the receptor dysregulation. Receptor subtype-specific dysregulation may explain regular HPGA function in patients as ERα appears responsible for inhibition of GnRH production, where ERβ and DHT activity exhibit stimulatory properties[119,120].

Why the syndromes appear selectively - a possible answer:

In the case of PSSD, although the necessity of a prolonged, slow withdrawal from antidepressants in order to avoid the presentation of syndromes has been suggested, the necessity of an equally slow and prolonged initiation has not been equally considered. If the above speculations are true, then the main factor in the appearance of the syndrome is not the abrupt discontinuation of the medication, but rather the abrupt initiation of it. It follows that the distinction between those who safely undergo SSRI treatment and those who do not, may be the inter-individual variation in the ability to adapt to homeostatic disruption or degree of disruption experienced by a certain dose of the medication. In essence, low responders, who usually need doses near the higher range of the spectrum for beneficial effects and experience little to no side effects may be unlikely to present with PSSD, whereas high responders, whose effective doses are near the lower end and have a hard time getting used to the medication are more likely to do so. This could explain the differences in dose and duration of treatment exhibited across patients, and provides a predictive link between medication response and appearance of post-medication symptoms.

Prolonged, slow initiation of SSRI treatment may help reduce this possibility in high responders.

Progesterone

Unlike the nature of the conclusions made so far on the aetiology of the syndromes, the role of progesterone in sexual behaviour is not speculative at all. Progesterone(P) plays a crucial but apparently dimorphic role in the facilitation or inhibition of sexual activity in men and women. The effects of progesterone seem to either facilitate or inhibit sexual behavior depending on a number of factors.

Exogenous P supplementation in healthy males consistently inhibits sexual activity across species[121]. As such, progesterone receptor agonists have been used to reduce deviant behavior in sex offenders[122]. Although some evidence exists of physiological levels of progesterone having minor modulatory effects[123], studies on complete absence of progesterone activity via Progesterone Receptor gene deletion demonstrated an significant increase, not decrease of male sexual behaviour[124].

In females, progesterone supplementation potentiates sexual behavior when administered after Estrogen priming, but inhibits it if administered prior, or at the same time with Estrogen. This effect appears to be time-dependant[125,126]. As in males, dose-dependant effects also appear in females, with supraphysiological doses again inhibiting sexual behaviours.[127,128,129] Contrary to the increases in sexual activity of male mice lacking the progesterone receptor, females of the same type are infertile, and exhibit significantly reduced sexual activity[130], demonstrating a vital role of progesterone in female sexual function.

Although the mechanistic functions of progesterone on sexual behaviour are not yet fully understood, its role in regulating sexual activity is evident, and overactivity of Progesterone seems to reliably inhibit sexual activity across genders[131].

The mechanisms that modulate these effects appear to be connected to both androgen and estrogen activity, but the relation to Estrogen is particularly interesting. Estrogen shows regulatory effects on Progesterone Receptors, with increases in E levels producing increases in PR expression[132,133,134]. Reduced estrogenic activity thus leads to reduced progesterone expression, and subsequently reduced P activity. Furthermore, the inhibitory effects of Progesterone have been attributed to an 80% decrease in locally-derived E2 uptake in the preoptic area[135]. Androgen uptake was unaffected. The mechanisms underlying these effects remain unknown. They might include down-regulation of E2 receptors, interference with aromatization, or a decrease in the ability of E2 receptors to bind E2 or to be transported into the nucleus. Studies have shown that Progesterone inhibits both aromatase expression and enzyme activity[136], exhibiting one of the possible regulatory effects on E2 uptake and local E2 production, the importance of which is known for facilitation of sexual behaviours. Another study has demonstrated the ability of progesterone to down regulate estrogen receptor expression[137].

These findings demonstrate the potential of Progesterone to be a significant factor in the inhibition of estrogenic activity across the syndromes. Progesterone levels have never been consistently measured in PSSD,PRSD or PFS patients. The significance and meaning of plasma levels, even if measured, would be arguable considering possible receptor expression downregulation. A single study on neuroactive steroids on patients previously treated with finasteride did exhibit discrepancies in Progesterone and its metabolites, which differed between cerebrospinal fluid and plasma[95].

At the presence of reduced estrogenic activity, Progesterone holds the ability to be significantly inhibiting of sexual function in both genders. At the same time, though effects or males are mainly inhibitory, a potential deficiency of Progesterone may be detrimental to sexual activity in women. Its dimorphic effect can be a factor of inconsistent results between genders when treatment is attempted and should be taken into consideration.

Pathways to treatment

As a result of everything discussed above, treatment should reflect the protocols that exhibit the highest success in restoration of sexual function after gonadectomy or other such disruptions in hormonal environment, and needs to account for differences between genders. The main factor however is going to be estrogen potentiation. Whether through directly increased levels of estrogen, or perhaps more preferably increases in aromatase activity, significant elevations in Estradiol levels need to be achieved in both genders, such that will allow for sufficiently increased estrogenic activity to modulate regulatory actions of Estrogen on ARs, ERs and PRs. Variations in how long each patient has suffered the syndrome, as well as in the degree of impairments, and current hormonal state necessitate differences in dosage, duration of treatment and medication selection. The goal should be a reorganisation in receptor expression and activity which will be followed by a rebalancing of hormonal levels, both of which will allow for a subsequent restoration of the pre-syndrome hormonal environment and endogenous production, and thus a persistent and independent from continuous hormonal supplementation recovery.

Below, a few different approaches to treatment will be outlined for both men and women separately.

In both men and women, oral administration of Estrogen will be inefficient due to first-pass metabolism of oral estradiol in the liver and its subsequent effects and should thus be avoided[138,139]. Liver metabolism, along with the presence of progestins or progestogens in contraceptives and HRT pills, is also the reason why oral HRT fails to relieve symptoms in women. Hormonal levels should be measured before initiation of any treatment and closely monitored:

- Total testosterone
- SHBG
- Albumin
- Sensitive Estradiol
- Free Testosterone

- Progesterone
- Prolactin
- PSA
- DHT

Other markers for ensuring safety and efficiency of treatment like lipids, liver function, blood count, etc. should be measured prior to treatment.

Men:

Because the HPGA operates on a negative feedback loop based on estrogenic activity, increases in Estradiol will inhibit secretion of GnRH and shut down the axis, leading to detrimental effects in fertility and production of androgen and other hormones. As a result, any increases in Estrogen need to be accompanied by a temporary replacement of androgens, along with maintenance of endogenous production in the testes. Intramuscular injections are the most dependable way to produce predictable effects and are necessitated. Testosterone is preferable as aromatization is desirable, but DHT can substitute it if need be. The ester of testosterone administered can vary but should be long-lasting to avoid the need of multiple daily injections. Doses will vary between patients but should be in the 120 to 200mg range for Testosterone and 500 to 1000iu of HCG, per week. These are TRT ranges. Estradiol administration will vary depending on amount and frequency necessary to produce recovery and minimise adverse effects. 2 to 4mg are good options for initial doses. Estradiol Ester should be of short to medium duration, to avoid averse reactions and control levels. Estradiol Benzoate or Valerate are good options. Treatment should be maintained until patient reports stability in recovery, ceased, and then followed by a clomiphene protocol to restore endogenous production and discontinue exogenous supplementation.

Example Protocol:

Estradiol Valerate(3mg) + Testosterone-Enanthate(150mg/week) + HCG(1000iu/week) Followed by: Clomiphene citrate 25 or 50mg ED or EOD depending on patient.

Additional options:

If TRT or injections need to be avoided, Mesterolone(Proviron) provides a good alternative for men. Mesterolone is a synthetic derivative of DHT. Mesterolone is taken orally, but is not metabolised in the liver, and thus liver toxicity is not a concern. Mesterolone binds to and activates the androgen receptor, with weaker androgenic potential than DHT. The main desirable effect of Mesterolone in this case will be its SHBG-binding property. Mesterolone has a very strong affinity for SHBG, potentially higher than DHT. Because of this, it will severely reduce the amount of Testosterone, DHT and Estradiol that are SHBG-bound. This increased amount in free levels of the above hormones will result in their increased activity. Thus mesterolone monotherapy is a viable alternative, but may not be as efficient as a full protocol.

Mesterolone can also be used in combination with TRT + hcg or HCG alone.

Example protocols:

Mesterolone 50mg ED + 2000iu HCG per week + 2mg estradiol valerate

Mesterolone 25mg ED + 100mg Test-E per week + 500iu HCG per week

Other combinations that achieve similar effects to the protocols above can be considered but are likely to be less effective.

Women:

Disruption in menstrual cycle is to be expected. Increase in androgens should be avoided in women, but may provide an alternative pathway if initial protocols appear inefficient, as aromatisation of Testosterone may be preferable to direct increases in Estradiol. Treatment in women should consist of an initial period of IM-administered Estrogen monotherapy, followed by a single administration of low-dose Progesterone after 10 days **and** only after patient reports beneficial effects from repeated Estradiol treatment. Dosing protocol in women consists of initial doses of between 4 and 10mg and frequency of up to 3 times a week depending on single dose amount and response. If the effects of progesterone appear deleterious, progesterone should be stopped and not administered again. Single administration of a progesterone antagonist such as Mifepristone could demonstrate whether reductions in Progesterone levels facilitate sexual behaviour, and thus guide direction of treatment. However, prolonged use of Mifepristone is not advised, as it appears to increase concentrations of plasma Progesterone, and may have unpredictable effects upon discontinuation.

After recovery is stabilised, a clomiphene protocol should replace Estradiol injections for a period of time, before it is ceased as well. Dosage of Estradiol will also vary but will be equal or slightly higher than those in men. Dosage of progesterone needs to be determined depending on outcomes.

Another possible pathway is the concomitant administration of Estradiol and low-dose Testosterone, as it has also shown to lead to full restoration of sexual behaviours. This should only be tried if progesterone resulted in deleterious effects.

A note on progesterone:

In cases where progesterone levels are initially found to be above physiological ranges, progesterone antagonists may be used to determine whether this overabundance in Progesterone has detrimental effects on sexual behaviour. In most cases however, estradiol supplementation should eventually regulate progesterone activity back to baseline.

Noteworthy mentions:

Follicle-stimulating hormone(FSH) may potentiate aromatase expression and activity[140]. A combination of HCG + FSH may prove useful in producing significant increases of Estradiol in men and women. And could provide an alternative treatment option. Increases in aromatase activity may also produce greater effects than direct E2 administration due to facilitation of tissue-specific production especially in brain areas related to sexual behaviour. Depending on the strength of this effect, FSH could be a useful tool.

Hops Extract (8-Prenylnaringenin / 8-pn) is the most potent phytoestrogen currently available. Inexpensive, available over the counter and so far proven safe and well tolerated, it is a good alternative towards increasing estrogenic activity, and can partially replace estradiol supplementation [141,142,143,144,145].

Concluding remarks

Besides putting an end to 3 different syndromes that have permanently ruined lives all across the world for decades, the observations and deductions made during the development of this theory hold the potential to bring about significant changes in the way we perceive estrogen and its role in both males and females. Most importantly, they differentiate estrogen as the definitive sex hormone, controlling sexual arousal and libido in both genders, whereas Testosterone facilitates sex-seeking behaviour and male characteristics, but not libido, sensitivity or arousal. This revised role of estrogen in male physiology would also explain the difficulty faced so far by endocrinological associations in determining the criteria of hypogonadism in men. The variations in Testosterone levels of men exhibiting hypogonadal symptoms can be explained if a majority of those symptoms are actually dependant on estrogen and not Testosterone. Furthermore, the distinct mechanism of aromatase through which the majority of Estradiol is synthesised in men, and the regulatory place of estradiol in the Hypothalamic Pituitary Gonadal Axis make possible a variation in its levels independent of the levels of Testosterone. These conclusions allow for the possibility that “andropause” **and** menopause, are primarily brought forth by decreases in estrogen levels. As such, they carry vast implications for the future of sexual health of both men and women.

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