Accutane – Link with ED/Sexual Dysfunction

5-alpha-reductase activity & ED/Sexual Dysfucntion

Gur, S., Kadowitz, P. J., & Hellstrom, W. J. (2013). Effects of 5-alpha reductase inhibitors on erectile function, sexual desire and ejaculation. *Expert opinion on drug safety*, *12*(1), 81-90.

Clinical trials with 5ARI report prevalence rates of de novo erectile dysfunction of 5 - 9%. Decreased circulating dihydrotestosterone (DHT) resulting from 5ARI use is associated with diminished sexual desire and/or orgasm. The presence of adverse sexual effects is associated with decreased self-esteem, quality of life and ability to maintain an intimate relationship. Inhibition of 5ARI additionally influences progesterone and deoxycorticosterone levels and may alter psychological functions, including increased depression, melancholy and loss of general well being.

Boudou, P., Soliman, H., Chivot, M., Villette, J. M., Vexiau, P., Belanger, A., & Fiet, J. (1995). Effect of oral isotretinoin treatment on skin androgen receptor levels in male acneic patients. *Journal of Clinical Endocrinology & Metabolism*,*80*(4), 1158-1161.

Excerpt: "*The present study clearly demonstrated a decrease in androgen receptor binding capacity... The isotretinoin-receptor complex may interact with cis-acting response elements in the promoter region of regulated genes, repressing the gene transcription encoding for the androgen receptor, the gene transcription encoding for the 5-alpha-reductase activity, or both transcriptions simultaneously*.

Öztekin, Ç. V., Gur, S., Abdulkadir, N. A., Lokman, U., Akdemir, A. Ö., Cetinkaya, M., & Hellstrom, W. J. (2012). Incomplete Recovery of Erectile Function in Rat after Discontinuation of Dual 5- Alpha Reductase Inhibitor Therapy. *Journal of Sexual Medicine*, *9*(7), 1773-1781.

In vivo erectile activity (intracavernosal pressure [ICP]/mean arterial pressure [MAP] and total ICP) in treatment groups were significantly decreased compared with controls

Traish, A. M., Hassani, J., Guay, A. T., Zitzmann, M., & Hansen, M. L. (2011). Adverse Side Effects of 5α- Reductase Inhibitors Therapy: Persistent Diminished Libido and Erectile Dysfunction and Depression in a Subset of Patients. *The journal of sexual medicine*, *8*(3), 872-884.

Prolonged adverse effects on sexual function such as erectile dysfunction and diminished libido are reported by a subset of men

Case study within this study;

"In 1999, a 24-year-old male was diagnosed with androgenetic alopecia (AGA). He had normal stature (height, 182 cm; weight, 80 kg), had no history of any medical illness, and was not taking any medications. He reported

having a normal sex drive and normal erectile capacity. He started treatment with finasteride (Propecia™), 1 mg daily, and within 2–5 days experienced soreness of the testicles, total lack of sex drive, and complete inability to achieve an erection. He had difficulty concentrating and felt depressed. Expecting these initial side effects to be temporary, he continued treatment. Except for some improvement of the soreness in the testicles, he felt numbness and there was no improvement in his sex drive or erectile function. After a little more than 1 month, he discontinued treatment and the side effects diminished to some degree, but sexual function never returned to normal. In the following months and years, the symptoms persisted with loss of libido and erectile dysfunction (ED). In 2003, the patient consulted a specialty clinic for sexual medicine in Boston, MA, USA, and went through extensive examinations. At this point, treatment with Viagra had been tried with only marginal success. Because of hopelessness and depression, two types of antidepressants (citalopram and bupropion) had been prescribed, which helped by “taking away the deepest lows,” but with no improvement in either libido or erectile capacity. In addition, there were undesirable side effects to these drugs and treatment was discontinued after several months. In Boston, the patient had a psychological evaluation and underwent duplex Doppler ultrasonography.
Suffering from persistent symptoms of ED, loss of libido, and depression, the patient consulted a clinic in Copenhagen, Denmark, which specializes in testosterone treatment. The total testosterone (T) varied between 22.6 and 14.2 nmol/L (651 and 409 ng/dL) in the baseline state. The fluctuations were felt to be quite wide. No 5 α-dihydrotestosterone (5 α-DHT) measurements were available. The following baseline tests were all found to be normal: sex hormone binding globulin, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, T3, T4, prolactin, estradiol, dehydroepiandrosterone sulfate (DHEA-S), and androstenedione. He is currently under no treatment, but 11 years later, he still suffers from ED and loss of libido.”

From scouring the internet for others with Accutane induced sexual dysfunction there are many that resemble this exact symptom set. Hormone testing shows no major abnormality and the individuals appear to be in good health otherwise. It appears from this that individuals have a type of androgenic resistance, thus explaining no help of treatment modalities such as testosterone replacement therapy. Also been noted that Viagra is of little use as the problem is not strictly to do with structural abnormalities such as vascular damage.

Tirado, S. A., & León, D. G. (2005). Erectile dysfunction during isotretinoin therapy]. *Actas urologicas españolas*, *29*(10), 974.

6 out of 20 (30%) of patients receiving isotretinoin developed erectile dysfunction during the study.

Erdemir, F., Harbin, A., & Hellstrom, W. J. (2008). 5- Alpha Reductase Inhibitors and Erectile Dysfunction: The Connection. *The journal of sexual medicine*,*5*(12), 2917-2924.

The connection between 5ARIs and sexual dysfunction is apparent upon review of the literature.

Propecia:
A drug used to treat hairloss as well as benign prostrate hyperplasia. It is a 5-alpha-reductase type I & II inhibitor and exhibits many similar side effects to isotretinoin in regards to sexual function. Isotretinoin seems to be only a 5AR type I inhibitor thus explaining how isotretinoin can exert only hypogonadal symptoms sexually as opposed to physically observable traits as well. This is due to the differing distributions of type I and II throughout the body.

http://www.propeciahelp.com/overview

A hypothesis as to why propecia is far more recognised for its sexual side effects more so than isotretinoin and more money invested into its research is possibly due to the age and thus credibility of victims. Propecia users are generally older men, who are financially stable and more mature than isotretinoin users who are generally to put it bluntly – spotty kids, not known for pro-activity nor being taken seriously in medical matters.

Similar Retinoids Expressing Similar Side Effects

Rossi, M., & Pellegrino, M. (2009). Acitretin-associated erectile dysfunction: a case report. *Cases journal*, *2*(1), 210.

Retinoids have been associated with male reproductive system dysfunctions in human and animal studies. Clinicians should be aware of the possibility of acitretin-induced erectile dysfunction.

Other Hypogonadol Side Effects

Ustun, I., Rifaioglu, E. N., Sen, B. B., Inam, M. U., & Gokce, C. (2013). Gynecomastia: a rare complication of isoretinoin?. *Cutaneous and ocular toxicology*, *32*(1), 93-94.

development of gynecomastia after isotretinoin treatment.

Persistence of Side Effects

Csoka, A. B., & Szyf, M. (2009). Epigenetic side-effects of common pharmaceuticals: a potential new field in medicine and pharmacology. *Medical hypotheses*, *73*(5), 770-780.

Quote;

Here we present the hypothesis that commonly-used pharmaceutical drugs can cause such persistent epigenetic changes. Drugs may alter epigenetic homeostasis by direct or indirect mechanisms. Direct effects may be caused by drugs which affect chromatin architecture or DNA methylation. For example the antihypertensive hydralazine inhibits DNA methylation. An example of an indirectly acting drug is **isotretinoin**, which has transcription factor activity. A two-tier mechanism is postulated for indirect effects in which acute exposure to a drug influences signaling pathways that may lead to an alteration of transcription factor activity at gene promoters. This stimulation results in the altered expression of receptors, signaling molecules, and other proteins necessary to alter genetic regulatory circuits. With more chronic exposure, cells adapt by an unknown hypothetical process that results in more permanent modifications to DNA methylation and chromatin structure, leading to enduring alteration of a given epigenetic network. **Therefore, any epigenetic side-effect caused by a drug may persist after the drug is discontinued.**

The following adverse effects have been reported to persist, even after discontinuing therapy, suggesting persistent (or perhaps slowly-reversing) gene expression changes and epigenetic effects: alopecia, arthralgias, ocular abnormalities, inflammatory bowel disease, keloids, osteopenia, hyperlipidemia, erectile dysfunction, and psychiatric disturbances. Isotretinoin is postulated to have complex effects on the brain and central nervous system."

Effects on Brain (brief)

Melcangi, R. C., Caruso, D., Abbiati, F., Giatti, S., Calabrese, D., Piazza, F., & Cavaletti, G. (2013). Neuroactive Steroid Levels are Modified in Cerebrospinal Fluid and Plasma of Post- Finasteride Patients Showing Persistent Sexual Side Effects and Anxious/Depressive Symptomatology. *The journal of sexual medicine*, *10*(10), 2598-2603.

(Once again a study on propecia, which shares some similar side effects to Accutane which we postulate is due to both acting as 5-alpha-reductase inhibitors)

"the most important finding was the comparison of their neuroactive steroid levels with those of healthy controls. Indeed, decreased levels of tetrahydroprogesterone, isopregnanolone and dihydrotestosterone and increased levels of testosterone and 17β-estradiol were reported in cerebrospinal fluid of postfinasteride patients. Moreover, decreased levels of dihydroprogesterone and increased levels of 5α-androstane-3α,17β-diol and 17β-estradiol were observed in plasma."

Bremner, J. D., Fani, N., Ashraf, A., Votaw, J. R., Brummer, M. E., Cummins, T., ... & Nemeroff, C. B. (2005). Functional brain imaging alterations in acne patients treated with isotretinoin. *American Journal of Psychiatry*, *162*(5), 983-991.

RESULTS: Isotretinoin but not antibiotic treatment was associated with decreased brain metabolism in the orbitofrontal cortex (–21% change versus 2% change for antibiotic), a brain area known to mediate symptoms of depression.

Kontaxakis, V. P., Skourides, D., Ferentinos, P., Havaki-Kontaxaki, B. J., & Papadimitriou, G. N. (2009). Isotretinoin and psychopathology: a review. *Ann Gen Psychiatry*, *8*(2).

strongly suggests a link between isotretinoin and psychopathology.

Strahan, J. E., & Raimer, S. (2006). Isotretinoin and the controversy of psychiatric adverse effects. *International journal of dermatology*, *45*(7), 789-799.

Isotretinoin disrupts the birth of new hippocampal cells.

Hippocampus is tied to the reward pathway.