Side Effects of 5-Alpha Reductase Inhibitors: A Comprehensive Review

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ABSTRACT

Introduction. 5α-reductase inhibitors (5ARI) include finasteride and dutasteride, and are commonly prescribed in the treatment of benign prostatic hyperplasia and androgenic alopecia. 5ARIs are associated with several known adverse effects (AEs), with varying reported prevalence rates.

Aim. The aim was to review and summarize findings from published literature detailing AEs associated with 5ARI use. A secondary aim was to review potential mechanisms of action, which may account for these observed and reported AEs.

Methods. A PubMed search was conducted on articles published from 1992 to 2012, which reported AEs with 5ARIs. Priority was given to randomized, placebo-controlled trials. Studies investigating potential mechanisms of action for 5ARIs were included for review.

Main Outcome Measures. AE data reported from available trials were summarized and reviewed.

Results. Reported AEs with 5ARIs include sexual dysfunction, infertility, mood disorders, gynecomastia, high-grade prostate cancer, breast cancer, and cardiovascular morbidity/risk factors, although their true association, prevalence, causality, and clinical significance remain unclear. A pooled summary of all randomized, placebo-controlled trials evaluating 5ARIs (N = 62,827) revealed slightly increased rates over placebo for decreased libido (1.5%), erectile dysfunction (ED) (1.6%), ejaculatory dysfunction (EjD) (3.4%), and gynecomastia (1.3%). The limited data available on the impact of 5ARIs on mood disorders demonstrate statistically significant (although clinically minimal) differences in rates of depression and/or anxiety. Similarly, there are limited reports of reversible, diminished fertility among susceptible individuals. Post-marketing surveillance reports have questioned the actual prevalence of AEs associated with 5ARI use and suggest the possibility of persistent symptoms after drug discontinuation. Well-designed studies evaluating these reports are needed.

Conclusions. 5ARIs are associated with slightly increased rates of decreased libido, ED, EjD, gynecomastia, depression, and/or anxiety. Further studies directed at identifying prevalence rates and persistence of symptoms beyond drug discontinuation are required to assess causality. **Trost L, Saitz TR, and Hellstrom WJG. Side effects of 5-alpha reductase inhibitors: A comprehensive review. Sex Med Rev 2013;1:24–41.**

Key Words. Prostate; Finasteride; Dutasteride; Adverse Events; Sexual Dysfunction

Introduction

5α-reductase inhibitors (5ARI) competitively inhibit the enzyme 5α-reductase (5AR), and include finasteride (Propecia 1 mg and Proscar 5 mg, Merck, New Jersey, USA) and dutasteride (Avodart 0.5 mg and Jalyn [dutasteride 0.5 mg and tamsulosin 0.4 mg], GlaxoSmithKline, London, UK). 5AR is responsible for conversion of several hormones as a rate-limiting step throughout multiple organ systems and tissues [1,2]. Currently, three subtypes of 5AR have been identified, with 5AR-1 and 5AR-2 being the most studied [3,4]. 5AR-1 has been identified in the central and peripheral nervous systems, including midbrain, pons, spinal cord, corpus callosum, anterior commissure, optic chiasm, as well as in the skin, liver, and to a lesser degree in the prostate. 5AR-2 is present in the liver, epididymis, prostate, seminal vesicles, penis, urethra, and testes [5–10]. 5AR-3 has been localized to multiple tissues and organ systems, with the highest expression

exhibited in the skin, kidney, liver, skeletal muscle, myometrium, and pancreas, and moderate expression in the testes, brain, breast, colon, and stomach [4,11].

Indications for Use

Due to abundant 5ARI activity in the prostate and skin, 5ARIs have been investigated predominantly for their effects on benign prostatic hyperplasia (BPH)-associated lower urinary tract symptoms (LUTS) and for the treatment of androgenic alopecia (AGA). Several trials of 5ARIs in men with BPH have demonstrated beneficial effects, including a reduction of prostatic volume, improved International Prostate Symptom Scores, improved urinary flow rates, decreased risk for acute urinary retention, and reduced need for BPH-related surgery [12–15]. Finasteride has further been shown to significantly improve and maintain hair counts in men with AGA [16–18].

Beyond the treatment of BPH-related LUTS and AGA, 5ARIs have been investigated for a role in the prevention of prostate cancer, particularly given the observation that congenital absence of 5AR eliminates the risk of subsequent prostate cancer development [19]. The outcomes and adverse effects (AE) relating to prostate cancer will be more thoroughly discussed later in this communication.

In addition to the beneficial effects listed above, 5ARIs may be associated with AEs, including sexual dysfunction (SD), infertility, cognitive/psychological dysfunction, gynecomastia, breast cancer, high-grade prostate cancer (HGPC), and cardiovascular risk factors/comorbidities. More recently, post-marketing surveys and publications have questioned whether the true prevalence and persistence of AEs following drug discontinuation have been underreported. These reports have subsequently led to regulatory labeling changes [20–25].

To evaluate the prevalence of AEs associated with 5ARI use, a PubMed search was conducted of all publications reporting AEs with finasteride and/or dutasteride from 1992 to 2012. Priority was given to randomized, controlled trials (RCT), with a pooled summary of effects performed for commonly reported AEs, including SD and gynecomastia. Less frequently reported AEs were reviewed based on available literature. Additionally, the current review provides limited discussion on potential mechanisms, which may account for the AEs observed.

Mechanism of Action

5ARIs functionally inhibit the 5AR enzyme, with finasteride predominantly inhibiting 5AR-2, and dutasteride inhibiting both 5AR-1 and 5AR-2 isozymes [3]. Finasteride crosses the blood brain barrier and impairs 5β-reductases, which function in hepatic synthesis and metabolism [26]. 5ARIs reduce plasma dihydrotestosterone (DHT) by 70–80% (finasteride) to >90% (dutasteride) and result in initial compensatory increases in T levels [13,15,27–30].

5AR is responsible for physiologic conversion of multiple hormones of testicular and adrenal origin, including testosterone (T) to DHT, progesterone to 5α-dihydroprogesterone (5α-DHP), and deoxycorticosterone to 5α-dihydrodeoxycorticosterone (5α-DHDOC). Each of these products is enzymatically modified by 3α-hydroxysteroid dehydrogenase (3AHSD) to convert DHT to 3α,5α androstane 17β-diol (3α-diol), 5α-DHP to 3α,5α-tetrahydroprogesterone (3α,5α-THP or allopregnanolone), and 5α-DHDOC to 3α,5α-tetrahydrodeoxycorticosterone (3α,5α-THDOC). See Figure 1 for graphical depiction of drug conversions, enzymes, and sites of action. These latter three products are categorized as neurosteroids, due to their role in neurological processes, with 5AR preferentially catalyzing a reaction with progesterone vs. T or androstenedione [6].

AEs

SD

5ARIs have a recognized, consistent association with sexual AEs, including decreased libido, erectile dysfunction (ED), and ejaculatory dysfunction (EjD). Among 27 RCTs reviewing the use of 5ARIs, reported ranges of decreased libido, ED, and EjD vary widely: drug: libido (0–65.4%), ED (0–67.4%), and EjD (0–60.4%); placebo: libido (0–59.6%), ED (0–61.5%), and EjD (0–47.3%) [12,13,15–18,31–51]. These widely discrepant results for both drug and placebo reflect differences in patient populations and study methodology. All cited studies obtained AE information through patient self-reporting and investigator review, with no prospective, placebo-controlled studies using targeted questionnaires, such as the International Index of Erectile Function (IIEF) or Male Sexual Health Questionnaire (MSHQ), among others. See Tables 1 and 2 for the summary of RCTs of 5ARIs reporting sexual AEs.