Review Article

5-alpha reductase inhibitors use in prostatic disease and beyond

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Abstract: 5-alpha reductase inhibitors (5-ARIs) are commonly used and widely available, with benefits observed from their effect on androgen signalling. Their effect relies on the inhibition of the 5-alpha reductase enzyme which aids in the conversion of testosterone to dihydrotestosterone. 5-ARIs have increasing clinical relevance outside of benign prostatic hyperplasia (BPH). Such development requires clinicians to have an updated review to guide clinical practices. This review details the pharmacology and mechanisms of action for 5-ARIs and how this relates to multiple clinical indications. Of note, is the debunked association between finasteride and increased risk of high-grade prostate cancer. Furthermore, adverse effects of 5-ARI use are detailed in this review, with specific mentions to post-finasteride syndrome. In addition to overviews pertaining to BPH and prostate cancer, much attention has also been focused on severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The androgen axis may be associated with an increased virulence for SARS-CoV-2 in men, with some reporting a correlation between the severity of illness and androgenic alopecia. Since these observations, the role of antiandrogens, including 5-ARIs, has been explored further in SARS-CoV-2. Increasing understanding of pathological processes involving the androgen axis in which 5-ARIs work, has led to increasing clinical indications for 5-ARIs. Several novel off-label indications have been suggested including its potential role in the pathogenesis of SARS-CoV-2, but to date, these claims have not been substantiated. Previously held truths regarding the role of 5-ARIs and prostate carcinogenesis have been contested, inadvertently leading to the re-exploration of 5-ARIs utility in prostate cancer. With growing evidence into pathological processes involving the androgen axis, 5-ARIs are likely to become increasingly more used. This review serves as a timely update of 5 ARIs pharmacology, current indications and potential future directions.

Keywords: 5-alpha reductase inhibitors (5-ARIs); review; prostate cancer; severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); coronavirus disease (COVID)

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Introduction

5-alpha reductase inhibitors (5-ARIs) are commonly used and widely available, with benefits observed from their effect on androgen signalling. Initially licenced for use in benign prostatic hyperplasia (BPH), finasteride and dutasteride are the two major 5-ARIs that are commercially available and in use today (1,2). Their effect relies on the inhibition of the 5-alpha reductase (5α-reductase) enzyme which aids in the conversion of testosterone to dihydrotestosterone (DHT) (3).

Since its introduction, the clinical indication for 5-ARIs has grown from BPH to include androgenetic alopecia (AGA) and hirsutism (1). As more pathological processes are identified as being mediated by DHT, the clinical

indications and utility of 5-ARIs expand. The relationship between 5-ARIs and prostate cancer is of particular interest due to the androgen-driven nature of prostate carcinogenesis (3,4). Other new associations have been observed between 5-ARIs and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), including with reduced disease severity and mortality (5,6).

With new developments and increasing clinical indications, an up-to-date review of 5-ARIs is warranted, helping to inform clinical practice. This narrative review addresses the mechanism of action of 5-ARIs, potential adverse effects, current clinical indications including indications within and outside of urology.

Pharmacology

Finasteride was first licenced by the United States Food and Drug Administration (US FDA) in 1992 (1,7). It competitively inhibits the type II 5α-reductase enzymes isoenzyme, suppressing serum DHT by approximately 70% from baseline (3). Dutasteride, the first dual 5α-reductase type I and type II isoenzyme inhibitor, was approved for use a decade later and is estimated to lower serum DHT by approximately 90% (8).

5α-reductase is a nuclear-bound steroid intracellular enzyme that converts the androgen testosterone into DHT. 5-ARIs are chemically 4-azasteroids that competitively bind 5α-reductase intracellularly, primarily in the prostate stroma, leading to the peripheral inhibition of testosterone conversion into its more potent metabolite. DHT is observed as having a greater affinity than testosterone to androgen receptors (AR) in the prostate gland. A hormonal mediator, DHT modulates genes responsible for cell proliferation and can lead to hyperplasia.

5α-reductase exists as two isoenzymes, type I and type II, primarily found within the prostate stroma. Type II isoenzymes are estimated to account for two-thirds of serum DHT production and can be found outside prostate tissue, including seminal vesicles, epididymides, hair follicles, and the liver (1). Finasteride selectively inhibits type II isoenzyme and reduces serum DHT by 65% within the first 24 hours (1). Dutasteride inhibits type I and type II, and was observed to reduce serum DHT by 90% after two weeks of regular dosing (2). DHT suppression through inhibition of 5α-reductase leads to an increase of serum testosterone of 15% and 19% for finasteride and dutasteride respectfully (1,2).

5-ARIs are absorbed well orally, with a mean bioavailability of approximately 60–65% from a 1 mg dosage (1,2). With 90% of the circulating drug being protein-bound, 5-ARIs are predominantly metabolised hepatically by the cytochrome P450 enzyme. It is estimated that between 32–46% of the drug is excreted in the urine, with the remaining 51–64% excreted in faeces. The half-life of 5-ARI is approximately 6 hours in young, healthy males, increasing to 8 hours in septuagenarians (1,2).

Adverse effects

Both finasteride and dutasteride are generally well-tolerated medications, with most adverse effects reported as mild and transient (2). The most frequently reported adverse effects are related to sexual dysfunction, mainly decreased sexual libido, impotence, and ejaculatory disorders. Increasing post-market reports of sexual and depressive side-effects prompted many countries to change labelling to include these adverse side effects. Despite a growing body of literature to support the existence of adverse sexual side effects, the validity of a causal relationship between 5-ARIs and all its reported adverse effects remains unclear, with only observation studies available (9-13). The Proscar Long-Term Efficacy and Safety Study (PLESS), reported a marginal effect with 3.7% of patients treated with finasteride ceasing the medication due to adverse sexual side effects, compared to 2.1% of patients taking placebo (14). A more substantial effect was observed in a meta-analysis by Liu *et al.*, where men taking 5-ARIs for BPH had 156% increased risk of experiencing sexual side effects (9). This study also observed dutasteride as having a greater incidence of adverse sexual side-effects than finasteride. Most literature suggests these symptoms tend to resolve within 1 month of ceasing the medication.

Several other adverse effects have been described, including depression, cardiovascular disease, and metabolic syndrome. Suggestions of an increase in the incidence of male breast cancer and dementia have not been supported by current literature (15,16). The association of 5-ARIs and depressive symptoms was first highlighted in the Prostate Cancer Prevention Trial (PCPT) (4). The PCPT however was not designed or powered to assess an association between depressive symptoms and 5-ARIs, failing to establish a causal relationship. Other studies attempting to correlate depressive symptoms and 5-ARIs have similar flaws, highlighted in a comprehensive clinical review by Saengmearnuparp *et al.* (17). It is reported 5-ARIs may increase insulin resistance, leading to high rates of diabetes, metabolic disease, and cardiovascular disease (18).

While only observation human data exists, these claims were supported by the pre-clinical findings in rodents by Livingstone *et al.*, where the absence of type I 5α-reductase isoenzyme was associated with hepatic steatosis and insulin resistance (19). This is in contrast to a previous publication by Hsieh *et al.*, where they report no association between 5-ARIs and cardiovascular events during a follow-up over 1,400 men over 5 years (20). This data however failed to examine markers of metabolic disease. Longer follow-up may be required. Currently, there remains no well-established relationship between 5-ARIs and metabolic syndrome or cardiovascular disease.

A growing chorus of consumers have reported persistent adverse side effects from 5-ARIs, despite its discontinuation of the medication. These persistent symptoms have been labelled post-finasteride syndrome (PFS), embodying a constellation of sexual, physical, and neuropsychiatric symptoms that developed during or after the use of 5-ARIs. Consequently, several countries, including the US FDA, have amended warnings to include the possibility of persistent side effects (21). The pathological mechanism of PFS is unclear, though it is theorised 5-ARIs inhibit the synthesis of neurosteroids known to affect mood, cognition and libido (17). Current literature is conflicting regarding the existence of PFS, along with the dosing and duration required to be at risk. The PLESS study showed 15% of patients taking finasteride experienced sexual side effects within the first 12 months, compared to 7% in the placebo group. During the remaining 3 years of follow-up, there was no difference in reported sexual side effects between groups (14). However, only 50% of people taking finasteride reported resolution of their adverse sexual side effects following discontinuation, compared to 41% in the placebo group. Recent meta-analysis on adverse side effects of 5-ARIs did not assess persistent symptoms. Current evidence in support of PFS consists of case reports, surveys or low volume observation data. It is, for this reason, that the existence, incidence and mechanism of PFS remain debated (13,21,22). To establish the existence of PFS, quality prospective data, including placebo trials, is required.

Benign prostatic hyperplasia

BPH prevalence and associated lower urinary tract symptoms (LUTS) increases with age, affecting 80% of men aged 70 and above. Like other sex-accessory organs, the prostate is responsive to hormones and growth factors secreted for maintenance. DHT mediates intracellular apoptosis and proliferation through AR, having the highest affinity and influence on prostatic tissue. Unlike prostate cancer, there are no alterations of AR expression in BPH.

5-ARIs inhibit DHT production and are indicated for the management of enlarged prostates >30 cc on imaging, a prostate-specific antigen level of >1.5 ng/dL or palpable prostatic enlargement on a direct rectal exam (23). Similarly, they are indicated to prevent LUTS progression and reduce the risk of acute urinary retention (AUR) or prostatic surgery. 5-ARIs can be used in the medical management of BPH as either monotherapy or in combination with alpha-blockers (24). The Medical Treatment of Prostate Symptoms (MTOPS) trial highlighted finasteride as having a 34% risk reduction in participants experiencing an American Urological Association symptom score increase of greater than 4 (P=0.002), and a 66% risk reduction for combination therapy (25). In a study across 36 months by Boyle *et al.*, finasteride reduced prostate volume by 27% compared to baseline and was found to improve urinary flow (Qmax) by 2.3 mL/s along with an increase of 3.6 points when the international prostate symptoms score (IPSS) was measured. The authors also observed that men with enlarged baseline prostates benefited the most from finasteride use with significant improvements in IPSS and Qmax metrics (26). In the PLESS, a double-blinded, placebo-controlled trial, men with symptomatic LUTS and enlarged prostates experienced improvements in symptoms (27). Finasteride reduced prostate volume by 18% compared to a 14% increase in the place group. Similarly, dutasteride has comparable results with a 57% and 55% risk reduction for AUR and BPH-related surgical intervention (28).

Patients and clinicians should expect maximal therapeutic efficacy in relieving LUTS approximately 6 months after commencing 5-ARI therapy. In the long-term, the MTOPS and Combination of dutasteride (Avodart) and Tamsulosin study (CombAT) 5-ARI monotherapy arms demonstrate 30% decrease in IPSS and 20% urinary flow at 4-year mark (14,25,29). As 5-ARI acts upon hormonal pathways, patients with larger baseline prostatic volumes experience the most clinical improvement. Patients with an initial prostatic volume of above 40 mL experience the most significant LUTS and urinary flow improvements (26). The ComBAT study findings cannot be extrapolated to smaller initial prostatic volumes of below 30 mL as it was not within the inclusion criteria.

The use of combination therapy is suggested for moderate to severe LUTS by the American Urological

Association (23). CombAT was a 4-year multicentre, randomised, double-blinded parallel-group study of 4,844 men ≥50 years of age with a clinical diagnosis of BPH, IPSS ≥12, and significantly enlarged prostates. The trial demonstrated that combination therapy of dutasteride and tamsulosin was significantly superior to tamsulosin monotherapy alone but not dutasteride monotherapy at reducing the relative risk (RR) of AUR or BPH related surgery occurrence (14). CombAT also reports that combination therapy provides greater benefit in superior results in disease progression compared to both monotherapies.

There are increasing surgical modalities to manage BPH; however, transurethral resection of the prostate (TURP) remains the historical gold standard. Patients progress to surgical management after unsuccessful combination therapy. Surgical management is recommended to patients with refractory LUTS, recurrent urinary tract infections, recurrent bladder stones or gross haematuria with bladder outlet obstruction, persistent urinary retention secondary to BPH or high-pressure retention (23,30). Prospective 5-ARI administration before TURP has been indicated to reduce the level of surgical bleeding (31). There are also associated decreases in transfusion rates and operating times. However, more established evidence through trials required to confirm these findings (32).

Beyond preoperative administration of 5-ARIs in reducing surgical bleeding, 5-ARIs have a role in reducing bleeding secondary to BPH-related gross haematuria. Local prostate angiogenesis is stimulated by vascular endothelial growth factors (VEGFs), a potent signalling protein that is up-titrated by androgens including DHT (33,34). Kearney *et al.* demonstrated finasteride as a suitable agent for improving gross haematuria secondary to BPH regardless of anticoagulation status through the suppression of DHT (35). In their retrospective review of 53 patients given daily 5 mg finasteride for BPH-related haematuria, 94% of patients experienced improving haematuria grading and 77% no longer experienced haematuria while taking finasteride. The study also appeared to identify a time-dependent relationship between prostate size and the duration required for finasteride to improve gross haematuria.

In vitro studies demonstrated finasteride interferes with angiogenesis and causes tissue hypoxia (36,37). In a study by Lekas *et al.*, 178 patients undergoing TURP were either allocated to finasteride or no medication prior to their operation (38). Blood loss was significantly elevated in the control group which received no medication. To assess for the impact of finasteride on BPH angiogenesis and tissue hypoxia, micro vessel density (MVD), VEGF, and hypoxia-inducible factor-1alpha (HIF-1α) were identified *in vivo* post-TURP. A statistically significant decrease in above factors was found in the tissue of patients on finasteride compared to those who were untreated.

Prostate cancer

The binding of androgen to AR leads to cell signalling resulting in prostate cell proliferation (39,40). By regulating prostate cell apoptosis and proliferation, androgens play a pivotal role in prostate cancer. The discovery and success of androgen deprivation therapy in treating prostate cancer caused the androgen-androgen receptor axis to be a prime target for new prostate cancer treatments. In the past, 5-ARIs have been suggested as potentially appealing prostate cancer chemopreventive agents, by inhibiting the conversion to the more potent DHT. The PCPT in the early 2000s demonstrated that 5-ARIs (finasteride), compared with placebo, had a 24.8% RR reduction in developing prostate cancer (4). However, their benefit was largely observed in low-risk disease and concerningly, a significant increase in proportion of high-grade prostate cancer was observed in men taking finasteride. Thompson *et al.* observed 37% of the graded prostate cancers to be Gleason score 7–10, compared to 22% of those in the placebo group, or a RR of 1.67 [95% confidence interval (CI): 1.44–1.93] (low-grade disease = Gleason ≤6; intermediate-grade disease = Gleason 7; high-grade disease = Gleason ≥8) (4). Given limited benefit in reducing significant disease and associated morbidity, 5-ARIs were never adopted or indicated as a chemopreventive agent for prostate cancer.

Since these initial findings, further research has been conducted to elucidate the relationship between 5-ARIs and prostate cancer. Findings have been mixed, though many studies have reported no discernible relationship between 5-ARIs and the incidence of high-grade prostate cancer (41-44). More recently, several notable meta-analyses have been conducted, all of which contend that 5-ARIs do not increase the incidence or risk of high-grade prostate cancer (45,46). Knijnik *et al.* examined the relationship between 5-ARIs and risk-stratified prostate cancer subgroups, meta-analysing 18 studies including ten randomised controlled trials (46). This meta-analysis observed no statistically significant difference between high-grade prostate cancer diagnoses and 5-ARI use (RR 0.98, 95% CI: 0.67–1.43,

I^2=75%). Furthermore, they observed no statistically significant difference in prostate cancer-specific mortality rates between the 5-ARI exposure arm and the control arm, a finding supported by three other meta-analyses, along with multiple other publications (42,43,45-51).

With multiple studies refuting the association of 5-ARIs and higher-grade prostate cancer, some have sought to explain the initial findings from the PCPT trial. Most theorise a sampling bias or detection bias has occurred in men using 5-ARIs, through 5-ARIs inhibiting indolent or low-grade tumours, falsely creating a higher proportion of more aggressive prostate cancers (52,53). Others suggest improved screening, with small prostate sizes from 5-ARIs leading to more accurate prostate-specific antigen testing, digital rectal examinations, and fewer sampling errors (54,55). Alternatively, the histological changes noted might mimic prostate cancer, an effect often seen with androgen deprivation therapy (53,56). Regardless, strong evidence suggests 5-ARIs have no significant impact on the incidence or mortality of higher-grade prostate cancers.

The potential for 5-ARIs to be used as chemopreventive medications should be re-examined. Multiple meta-analyses have confirmed a relationship between 5-ARIs and prostate cancer, with both finasteride and dutasteride reducing the incidence of overall and lower-grade prostate cancers (45,46,49,50). Knijnik *et al.* observed a RR reduction of 24% for low and intermediate-risk prostate cancer cohorts [RR 0.76, 95% CI: 0.59–0.98, I^2=0.74%], a similar finding to the PCPT observations (4,46). Another study reported a RR reduction of 16% in all prostate cancers (RR 0.84, 95% CI: 0.74–0.94) and 27% in low-grade prostate cancers (RR 0.73, 95% CI: 0.60–0.88) (49). Recent publications have even suggested 5-ARIs have a potential benefit in preventing the clinical and pathological progression of prostate cancer, as is observed by the meta-analysis by Yang *et al.* (47).

With the potential for increased use of 5-ARIs in men with prostate cancer, clinicians must remain cognisant of their effect on prostate specific antigen (PSA) screening and surveillance. PSA is released by the epithelial cells of the prostate to aid the mobilisation of semen. In prostatic diseases such as BPH and prostate cancer, elevated PSA levels are a consequence of epithelial disruption leading to increased stromal and serum uptake (57). 5-ARIs inadvertently suppress serum PSA values within 6 months of continuous use, while poorly understood it is thought by preventing the production of DHT they limit new growth and reduce epithelial disruption (58-60). The American Urological Association suggested expecting approximately a 50% decrease in serum PSA among men using 5-ARIs (4,61). These guidelines are in line with a 2021 systematic review and meta-analysis by Sakalis *et al.*, observing a comparable reduction in PSA when compared to dutasteride (62). However, Sakalis *et al.* observed finasteride reduced PSA levels by –0.62 [95% CI: –0.71 to 0.56], suggesting an underestimation when compared to conventional teaching. These findings are yet to influence current practice, where PSA values among men using 5-ARIs are routinely doubled before their application into various screening or surveillance protocols.

With substantial evidence refuting the association of 5-ARIs and high-grade prostate cancer, and proven benefits in reducing the overall incidence of prostate cancer, the lack of clinical indication for 5-ARIs as a chemopreventive agent in prostate cancer should be re-examined. More prospective data is warranted prior to further consideration of this application.

SARS-CoV-2

Despite comparable infection rates between men and women, men have been disproportionately affected by the SARS-CoV-2 with increased severity of illness and higher mortality rates (63). The pathological and immunological process leading to this discrepancy is not well elucidated. However, much attention has been focused on the androgen axis as the cause for this increased virulence in men, with some reporting a correlation between the severity of illness and androgenic alopecia (64). Since these observations, many have investigated the role antiandrogens may play, including 5-ARIs, in SARS-CoV-2.

Several publications have identified a protective benefit from antiandrogens in men with SARS-CoV-2. Potential benefits include lesser symptoms, reduced disease severity and fewer intensive care unit (ICU) admissions (5,6,65,66). These claims have been refuted in a recent meta-analysis, where there was no evidence for a protective benefit of androgen deprivation therapy from SARS-CoV-2 (67).

While the majority of research has dealt with androgen deprivation therapy, several studies have assessed the impact of antiandrogen therapy on SARS-CoV-2, with three directly addressing the potential impact of 5-ARIs (6,66,68). Most notably, Cadegiani *et al.* reported that men taking dutasteride had a shorter duration of illness, along with higher virologic and clinical remission rates on day seven of their illness when compared to a placebo group in their double-blinded randomised controlled trial. Participants

were seen in an outpatient setting having confirmed with SARS-CoV-2 on PCR testing and subsequently randomised into either dutasteride (n=44) or placebo (n=43) arms of the trial where they were treated for 30 days or until complete resolution of their symptoms. Here they reported a higher virologic remission rate (64.3% versus 11.8%; P=0.0094) and higher clinical recovery rate (84.7% versus 57.5%; P=0.03) in the men taking dutasteride. A matched paired analysis of 944 participants, had similar findings where the absolute risk of infection on a community acquired SARS-CoV-2 infection was significantly lower in men taking 5-ARIs. They reported a RR for men taking 5-ARIs as 42.3% (399/944), compared to the paired group at 47.2% (446/944). This equated to an absolute risk reduction of 4.9% [odds ratio (OR) 0.81, 95% CI: 0.67–0.97, P=0.026]. Similarly, 77 men were followed during a prospective cohort study, where a lower proportion of ICU admissions was observed among men taking anti-androgens including 5-ARIs, [1/12 (8%) compared to 38/65 (58%), P=0.0015]. The study however reported a number of limitations, including small sample size and use of multiple anti-androgen medications with variable mechanisms of actions. These results are however encouraging, with the further investigation needed to establish the utility of 5-ARIs and their influence in the management of SARS-CoV-2.

While the exact biologic interplay between androgens and SARS-CoV-2 is unknown, it is hypothesised that SARS-CoV-2 binds with the angiotensin-converting enzyme 2 (ACE2) and enters pulmonary tissues via its spike protein after activation by transmembrane protease serine 2 (TMPRSS2) (69). Both proteins are androgen-regulated, though TMPRSS2 is particularly sensitive, with increased expression in malignant prostatic tissue (70). Higher androgen levels lead to upregulation of TMPRSS2 and theoretically increase the risk of cell-virus fusion. This association between androgens and SARS-CoV-2 is supported by the rates of hospital admissions for prepubescents and men with AGA, with lower and higher rates respectfully (71,72).

Pro-immune effects associated with oestrogen is an alternative premise (66,73). It is postulated that by inhibiting the enzymatic conversion of testosterone to DHT, the overall concentration of serum androstenedione produces a physiological shift to produce greater amounts of oestrogen. Oestrogen is known to have a pro-immune effect, in contrast to testosterones immunosuppressive effect (74).

Further study is required for 5-ARIs and their influence on pathological processes for SARS-CoV-2. Currently, the role of androgens in mediating TMPRSS2 in lung parenchyma is conflicting (75,76). Further, the pro-immune effects of elevated oestrogen have been refuted by the claim that any associated effects of increased oestrogen concentrations directly compete with the immunosuppressive effect of elevated testosterone (66).

Unlike testosterone and oestrogen, the TMPRSS2 expression theory and elevated oestrogen theory are not competitive. It is therefore possible that both proposed mechanisms of action work synergistically. Nonetheless, presently 5-ARIs are not indicated for use in preventing or managing SARS-CoV-2 due to limited prospective data.

Other non-urological indications for 5-ARIs

AGA is a form of hair loss experienced by both men and women, commonly referred to as ‘pattern baldness’, with each sex experiencing distinct distributions of hair loss. The pathological process involves hair follicles undergoing miniaturisation, referring to the production of more delicate hairs that readily fall out due to their fragile shafts (77). While the molecular process of AGA is a mystery, it is known to be mediated by DHT, evidenced by its absence in men with a 5α-reductase type II deficiency (78). As previously highlighted, two isoenzymes exist, type I located in the liver and skin, including the scalp, and type II located in hair follicles and the prostate. Commercially sold as ‘Propecia’, finasteride was first approved by the FDA in 1997 to treat AGA (1). Oral administration of finasteride has robust literature to support its use. The use of topical finasteride avoids the unwanted systemic side-effects of oral 5-ARI use and appears to be comparable to oral finasteride, though more quality long-term studies are needed (78). Dutasteride is also indicated for the treatment of AGA with some suggesting its superiority, though limited data exists comparing it to finasteride (77,79).

5-ARIs are increasingly used in hirsutism, a condition where predominantly women present with excessive hair growth (80). Excess circulating androgens stimulates terminal hair growth over androgen dependent areas. The excess hair growth is often course, like sexual or secondary hair such as those seen in male growth patterns (80,81). While often presenting as primary idiopathic Hirsutism, numerous aetiologies can lead to excess androgen production and therefore the development of hirsutism, including polycystic ovarian syndrome, acromegaly, prolactinemia or thyroid disfunction (82).

There has been increasing preclinical studies examining the benefits of 5-ARIs on reducing excessive alcohol intake in men. It is hypothesised that endogenous neuroactive steroidal properties of 5-ARIs may mediate sedative effects like alcohol in adult men (83). This is based on weak evidence presuming that 5-ARIs may reduce drinking due to its impacts on neuroactive steroids concentrations.

The role of 5-ARI for stuttering priapism is also of interest currently. This recurrent form of ischaemic priapism consists of undesirable, painful erections that last for less than 3 hours, with debilitating impacts on quality of life. Evidence for dutasteride is a promising as an emerging intervention for stuttering priapism. Daily dutasteride with consequent tapering was demonstrated to reduce episodic frequency without significant side effects (84).

Conclusions

Since their introduction in 1992 for the management of BPH, the clinical indications for 5-ARI have expanded to areas such as androgenic alopecia and hirsutism. This can be attributed to the increasing understanding of pathological processes involving the androgen axis in which 5-ARIs work. Several novel off-label indications have been suggested including its potential role in the pathogenesis of SARS-CoV-2, but to date these claims have not been substantiated. Previously held truths regarding the role of 5-ARIs and prostate carcinogenesis have been contested, inadvertently leading to the re-exploration of 5-ARIs utility in prostate cancer. Other future directions will continue to be elucidated, as the implications of 5-ARIs in androgen signalling continues to be explored.

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Footnote

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