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https://doi.org/10.1016/j.jaad.2024.03.017

Sexual dysfunction with 5-alpha-reductase inhibitor therapy for androgenetic alopecia: A global propensity score matched retrospective cohort study

To the Editor: 5-alpha-reductase inhibitors (5-ARIs) are a therapeutic mainstay for androgenetic alopecia (AGA). Uncertainty exists surrounding sexual dysfunction (SD) associated with 5-ARIs. Meta-analyses examining associations between 5-ARIs and SD demonstrate conflicting results (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/nfsydtdcsm.1).[1-4] Prior analyses involved predominately pooled data from trials. Currently, there is a paucity of population-level data investigating 5-ARI and SD. Here we evaluate potential associations of 5-ARIs with SD in a global population.

A retrospective cohort study was conducted analyzing patients with AGA in TriNetX, a health research network with electronic medical record data from 120 million patients worldwide; 59,473 male patients with AGA were extracted (Supplementary Fig 1, available via Mendeley at https://doi.org/10.17632/nfsydtdcsm.1). Patients with any history of benign prostatic hyperplasia or unclear timeline of 5-ARI prescription were excluded (n = 36,136); 23,337 included patients were split into 2 cohorts, those prescribed 5-ARI within 1 month of AGA diagnosis (n = 10,585), and those with no history of 5-ARI inhibitor (n = 12,572) (Supplementary Table II, available via Mendeley at https://doi.org/10.17632/nfsydtdcsm.1). A risk analysis was undertaken calculating the risk of developing SD up to 1 year after 5-ARI prescription for AGA. Propensity score matching was implemented balancing for confounders.

Of 10,585 5-ARI exposed patients (mean age 39), 289 (3%) experienced SD with an absolute risk increase of 0.97% compared to 5-ARI naïve patients (95% CI 0.528%, 1.413%; $P < .001$) (Table I). On subanalysis by dosage/agent, the only significant risk increase found was patients with AGA on finasteride 5 mg vs no 5-ARI (Table I).

In 5-ARI exposed patients with SD, prevalence of the following comorbidities was significantly elevated compared to those without SD: obesity, nicotine dependence, diabetes mellitus, hypertension, mood, and anxiety disorders ($P < .0001$) (Table II). Patients with these factors were excluded independently and a decrease in absolute risk increase was seen but was still significant (Table I). Once patients with any of these comorbidities were excluded from risk analysis, the absolute risk increase for 5-ARI exposed patients was reduced to 0.43 compared to 5-ARI naïve patients (95% CI −0.02%, 0.885%; $P = .061$).

Data investigating comorbidities in 5-ARI AGA patients are limited. The previous cohort study investigating these factors found hypertension, depression, smoking, obesity, and diabetes mellitus all contributed to risk of SD.[5] Results here align with these prior findings, demonstrating an initial significant increase in risk of SD with 5-ARI which lost significance once patients with any of the 6 previously mentioned comorbidities were excluded. Of note, because many of these chronic comorbidities affect patients after 5-ARIs are stopped, these results may contribute to a working hypothesis for persistent SD after 5-ARI discontinuation, a subject debated in literature and media.

Limitations include the retrospective nature of this study, potential for documentation errors, and underreporting of SD as patients require a follow up visit for documentation. However, this study analyzes over 23,000 real-world patients with robust external validity while controlling for confounders in a way not feasible in other study types of this size.

Ultimately comorbid factors may play a significant role in SD associated with 5-ARIs. The findings of this study emphasize the importance of medical history in determining candidacy for 5-ARIs to reduce SD related adverse events.

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Funding sources: None.

Patient consent: Not applicable.

IRB approval status: Data accessible via TriNetX only contains anonymized information as per

Table I. Propensity score matched risk analysis of sexual dysfunction in patients with 5α-reductase inhibitor and without 5α-reductase inhibitor

Category	SD in exposed	SD in control	Risk with exposure	Risk without exposure	Risk difference	95% CI	*P* value	Risk ratio	95% CI	Odds ratio	95% CI
5-ARI any dose vs no 5-ARI	289	227	2.89%	1.92%	0.97%	(0.528%, 1.413%)	<.0001	1.505	(1.247, 1.817)	1.52	(1.254, 1.843)
Finasteride 5 mg vs no 5-ARI	43	237	3.04%	1.66%	1.37%	(0.254%, 2.493%)	.0166	1.826	(1.107, 3.013)	1.852	(1.11, 3.09)
Finasteride 1 mg vs no 5-ARI	94	227	2.74%	2.19%	0.55%	(−0.204%, 1.304%)	.153	1.251	(0.919, 1.703)	1.258	(0.918, 1.725)
Dutasteride vs no 5-ARI	10	237	3.75%	3.82%	−0.07%	(−3.323%, 3.18%)	.9656	0.981	(0.415, 2.318)	0.981	(0.401, 2.396)
Finasteride any dose vs dutasteride	10	278	9.52%	9.80%	−0.28%	(−8.332%, 7.772%)	.9456	0.971	(0.422, 2.235)	0.968	(0.385, 2.435)
Finasteride 1 mg vs 5 mg	38	94	2.67%	3.06%	−0.38%	(−1.689%, 0.92%)	.5635	0.874	(0.554, 1.38)	0.871	(0.545, 1.393)
Any 5-ARI vs no 5-ARI comorbidity subanalysis											
Hypertension excluded	216	163	2.55%	1.80%	0.75%	(0.294%, 1.21%)	.0013	1.417	(1.145, 1.755)	1.428	(1.148, 1.777)
Diabetes excluded	263	197	2.70%	1.88%	0.83%	(0.381%, 1.269%)	.0003	1.44	(1.182, 1.754)	1.452	(1.187, 1.777)
Smoking excluded	248	187	2.61%	1.74%	0.87%	(0.429%, 1.303%)	.0001	1.498	(1.219, 1.839)	1.511	(1.225, 1.864)
Obesity excluded	256	180	2.62%	1.67%	0.95%	(0.514%, 1.387%)	<.0001	1.569	(1.273, 1.934)	1.585	(1.28, 1.961)
Mood disorders excluded	181	155	2.25%	1.73%	0.53%	(0.079%, 0.979%)	.0214	1.307	(1.04, 1.642)	1.314	(1.041, 1.658)
Anxiety disorders excluded	158	124	2.17%	1.39%	0.78%	(0.329%, 1.228%)	.0007	1.56	(1.204, 2.022)	1.572	(1.208, 2.047)
All 6 above comorbidities excluded	85	74	1.56%	1.13%	0.43%	(−0.02%, 0.885%)	.061	1.383	(0.984, 1.946)	1.389	(0.983, 1.963)

5-ARI, 5-alpha-reductase inhibitor; *CI*, confidence interval; *SD*, sexual dysfunction.

Table II. Baseline characteristics of patients with 5α-reductase inhibitor with any history of sexual dysfunction and without any history of sexual dysfunction

Column1	SD	No SD	*P* value
N	687	9898	
Mean age	46.8	39.1	<.0001
Ethnicity			.191061667
Non-Hispanic or Latino	632 (92%)	9205 (93%)	
Hispanic or Latino	55 (8%)	693 (7%)	
Race			<.0001
White or Caucasian	522 (76%)	7226 (73%)	
Black or African American	27 (4%)	297 (3%)	
Asian	41 (6%)	594 (6%)	
American Indian or Alaska Native	7 (1%)	40 (0.4%)	
Native Hawaiian or other Pacific Islander	7 (1%)	14 (0.14%)	
Unknown race	82 (12%)	1683 (17%)	
Comorbid conditions			
Obesity, unspecified	103 (15%)	891 (9%)	<.0001
Diabetes mellitus	96 (14%)	594 (6%)	<.0001
Personal history of nicotine dependence	110 (16%)	791 (8%)	<.0001
Essential (primary) hypertension	254 (37%)	1683 (17%)	<.0001
Heart failure	21 (3%)	99 (1%)	<.0001
Peripheral vascular disease, unspecified	21 (3%)	98 (1%)	<.0001
Atherosclerosis	14 (2%)	48 (0.5%)	<.0001
Personal history of malignant neoplasm of genital organs	13 (2%)	30 (0.3%)	<.0001
Mood [affective] disorders	254 (37%)	2277 (23%)	<.0001
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	344 (50%)	3167 (32%)	<.0001
Schizophrenia, schizotypal, delusional, and other nonmood psychiatric disorders	28 (4%)	198 (2%)	<.0001
Epilepsy and recurrent seizures	14 (2%)	99 (1%)	<.0001
Procedures: Surgical Procedures on the male genital system	48 (7%)	395 (4%)	<.0001
Medication history			
Antidepressants	323 (47%)	2870 (29%)	<.0001
Anticonvulsants	131 (19%)	988 (10%)	<.0001
Antipsychotics	82 (12%)	69 (7%)	<.0001
Sildenafil	391 (57%)	396 (4%)	<.0001
Tadalafil	254 (37%)	197 (2%)	<.0001

SD, Sexual dysfunction.

the deidentification standard defined by the US Health Insurance Portability and Accountability Act (HIPAA) in section §164,514(a). Given this study used only deidentified data and did not involve individually identifiable patient data, this study was exempt from institutional review board approval.

Key words: 5-alpha-reductase inhibitor; androgenetic alopecia; dutasteride; epidemiology; erectile dysfunction; finasteride; pharmacology; sexual dysfunction.

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Conflicts of interest

None disclosed.

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https://doi.org/10.1016/j.jaad.2024.03.019

Dermatologic findings associated with semaglutide use: A scoping review

To the Editor: Recent studies on semaglutide, a glucagon-like peptide-1 agonist, have shown its broad applicability and effectiveness in reducing cardiovascular risk in individuals with obesity, inducing sustained weight loss, and improving glycemic control in type II diabetes.[1-3] However, few studies have characterized skin findings in patients on this medication. Through this scoping review, we aim to investigate reported dermatologic adverse events associated with both subcutaneous and oral administrations of semaglutide.

We conducted a scoping review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, utilizing PubMed, Embase, and Scopus databases on articles reporting dermatologic findings associated with semaglutide published until January 2024. Search strings were used to identify articles from these databases (Supplementary Methods, available via Mendeley at https://data.mendeley.com/datasets/3mxh852x4p/1). Duplicates were removed, and 2 authors independently extracted the data (M.M.T., A.C.L.). Uncertainties or discrepancies were discussed among these 2 authors, and a consensus was reached. Studies that specified another drug as the cause of the described adverse event were excluded.

A total of 22 articles (15 clinical trials, 6 case reports, and 1 retrospective cohort study) were included (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/djcggf9855/1). These articles describe semaglutide-associated dermatologic adverse events in 255 patients (Table I). Injection site reactions occurred in 3.5% of patients taking semaglutide; however, this was lower than the rate in the placebo and comparator groups (6.7%). For all other reports, adverse events were more frequently observed with semaglutide than the placebo or comparator groups. Oral administration of semaglutide 50 mg was associated with altered skin sensations, such as dysesthesia, hyperesthesia, neuralgia, pain of the skin, paresthesia, sensitive skin, and a skin burning sensation. In addition, alopecia was reported in 6.9% of patients on oral semaglutide 50 mg weekly compared to 0.3% of patients taking the placebo; however, only 0.2% of patients on subcutaneous semaglutide 2.4 mg had alopecia compared to 0.5% on placebo. Two cases of keratinocyte carcinoma were reported out of 258 patients at risk compared to no cases in the placebo or comparator groups. Several case reports documented isolated cases of severe events, such as angioedema, bullous pemphigoid, dermal hypersensitivity, eosinophilic fasciitis, and leukocytoclastic vasculitis, that led to discontinuation of semaglutide. Bullous pemphigoid, leukocytoclastic vasculitis, and eosinophilic fasciitis resolved days to months after discontinuation of the medication. Treatment of semaglutide-associated eosinophilic fasciitis also required immunosuppression.

In this study, higher rates of alopecia and altered skin sensations were seen in individuals on oral semaglutide. Variations in dosage and administration routes could influence the types and severity of skin findings, underscoring the need for additional research. There have also been isolated cases of severe dermatologic adverse events, including angioedema, bullous pemphigoid, eosinophilic fasciitis, and leukocytoclastic vasculitis, which should be noted as possible side effects. To date, there are no semaglutide-associated safety reports within the Food and Drug Administration MedWatch database. Limitations include the inability to control for confounding factors and establish a direct causal association between semaglutide and the adverse events. Notably, significant *P* values do not indicate causation. Further investigation into the underlying mechanisms and risk factors of these adverse events are needed.

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Funding sources: None.

Patient consent: Not applicable.

IRB approval status: Not applicable.