Sexual dysfunction in men taking systemic dermatologic medication: A systematic review

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Background: Prescription medications are among the most common causes of sexual dysfunction, and patients are often hesitant to seek help when experiencing these symptoms.

Objective: In this review, we identify the available evidence of sexual adverse effects in men using systemic dermatologic medications and suggest screening protocols and actions that may improve a patient's symptoms where possible.

Methods: A systematic review was conducted of all articles in the PubMed database published from the time of inception to May 2018 to identify studies evaluating the use of systemic dermatologic medications in men with evidence of sexual adverse effects. Subsequently, a secondary in-depth literature review was performed for each individual medication.

Results: There were 5497 articles reviewed in the primary systematic review, and 59 articles covering 11 systemic dermatologic medications met inclusion criteria. We identified level 1 evidence for sexual adverse effects as a primary outcome in patients taking finasteride.

Limitations: Many included studies were limited by sample size and methodology.

Conclusion: The information in this review may serve as a reference of adverse effects when deciding on a therapeutic agent and a guide to help identify patients to screen for sexual dysfunction. (J Am Acad Dermatol 2019;81:163-72.)

Key words: anorgasmia; ejaculation dysfunction; erectile dysfunction; impotence; libido; sexual dysfunction; systemic medications.

Sexual health in men is made up of several components, including sexual desire or libido, erection, orgasm, and ejaculation. Each may be compromised by a variety of pathologies and substances, such as medications and alcoholism, depression, relationship issues, systemic illness (eg, diabetes mellitus, cardiovascular disease), and testosterone deficiency.

Impaired sexual function is common and frequently attributed to increasing age but can affect men of all ages.[1] In men aged 18 to 59 years, 31% reported sexual dysfunction; therefore, a good medical history and examination are judicious in all patients to evaluate for any treatable causes.[1] Furthermore, prescribed medications are the frequently cited cause.[2] For this reason, physicians should be aware of the potential for these adverse effects when prescribing treatment regimens and should discuss the possibility for adverse reactions with their patients. This information is well described for antihypertensive and psychotropic drugs[3] but is poorly described within dermatologic literature. To

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facilitate patient-provider discussions, we review the available evidence of sexual adverse effects in men using systemic dermatologic medications and offer potential alternative therapies.

METHODS

To identify systemic dermatologic medications used in men with evidence of sexual adverse effects, an initial electronic literature search was conducted of all articles in the PubMed database published from the time of its inception through May 2018. The Medical Subject Headings terms "male," "medication," and "medication/adverse effect" were combined with each of the following terms representing the different parameters of sexual dysfunction: sexual dysfunction, erectile dysfunction, libido, pituitary disease, orgasm, penile erection, and ejaculation.

Studies were included if they met the following criteria: (1) subset of patients taking 1 United States Food and Drug Administration–approved systemic dermatologic medication in isolation, (2) description of male sexual adverse effects of identified medication, and (3) available in English or Spanish. Studies were excluded using the following criteria: (1) duplicate publications, (2) abstracts or presentations, (3) review or expert opinion without clinical appraisal, (4) included a subset of patients taking multiple medications, (5) inclusion of only female patients, (6) use of only animal models, or (7) study evaluated through an included meta-analysis. In the event meta-analyses included duplicate publications, preference was given to the larger meta-analysis.

For each medication with studies identified through systematic review, a secondary in-depth literature review was performed to ensure inclusion of all pertinent studies. The name of each medication combined with "sexual side effects" was searched in the PubMed database, and the references of all included studies were reviewed to list missing articles. All additional studies meeting the above exclusion criteria were included in the review. After confirmation of medications with sexual adverse effects, alternative agents for the same indications were identified, and a subsequent PubMed database search combining the name of the alternative agent combined with "sexual side effects" was conducted to rule out evidence of sexual adverse effects with these medications. All included randomized trials were assessed for risk of bias using the Cochrane risk of bias tool.

CAPSULE SUMMARY

- Prescription medications are a common cause of sexual dysfunction. Possible sexual adverse effects should be discussed with men using these medications.
- We identified evidence for sexual adverse effects in patients taking 11 systemic dermatologic medications. Level 1 evidence evaluating sexual dysfunction as a primary outcome was available for finasteride.

RESULTS

During the initial search, 5497 articles covering 377 medications were reviewed. After the inclusion criteria were applied, 29 studies were included in this review (Fig 1) describing 10 systemic dermatologic medications—acitretin, corticosteroids, cyclosporine, finasteride, gabapentin, isotretinoin, itraconazole, methotrexate, pregabalin, and thalidomide (Table I).[4-56] A secondary literature search identified an additional 30 studies. Case reports and case series are summarized in Supplemental Table I (available on Mendeley), and randomized trials (including bias assessment), case-control studies, and cohort studies are described in Supplemental Table II (available on Mendeley).

5α-Reductase inhibitor

Finasteride. Although there is some evidence against sexual dysfunction occurring in patients taking 5 mg and 10 mg[57] of finasteride, most studies describe relatively common adverse effects of decreased libido, impotence, and ejaculation disorders.[4-7,18,58-60] However, these doses are rarely used in dermatology and are typically used to treat benign prostatic hyperplasia—a strong predictor for the development of treatment-related erectile dysfunction (ED).[8]

Among men taking 1 mg finasteride for androgenic alopecia, the evidence for sexual adverse effects is less conclusive. We identified 5 studies that did not support the increased rates of sexual dysfunction in men taking 1 mg finasteride for androgenic alopecia.[9,61-64] However, we feel that the evidence describing increased rates of sexual dysfunction is more compelling. We identified 10 studies demonstrating sexual adverse effects, including ED and decreased libido, in patients taking 1 mg finasteride.[10-15,17,19-21]

In studies addressing reversibility, most of these patients have resolution of sexual adverse effects after discontinuation of finasteride, and many have improvement of adverse effects over time with continued finasteride use. However, some studies

Abbreviations used:

ED: erectile dysfunction
NSAID: nonsteroidal anti-inflammatory drug

describe a subset of patients with persistent adverse effects after discontinuation. Three studies identified in this review describe complete reversibility of sexual dysfunction in all patients,[7,12,19] but 11 studies[4,8,10,11,17,21-36] describe patients experiencing irreversible adverse effects. These findings were most convincing in a retrospective review of 11,909 patients that identified 167 with persistent ED (1.4% of the cohort vs 31.5% of patients with treatment-related ED). The strongest predictors for the development of these symptoms were prostate disease, duration of therapy, age, and nonsteroidal anti-inflammatory drug (NSAID) use. Interestingly, in patients of all ages who took ≤1.25 mg/d, NSAID use conferred a 4.8-times higher risk of developing persistent symptoms.[8] For this reason, we advise increased screening for sexual dysfunction among patients taking NSAIDs and finasteride concurrently.

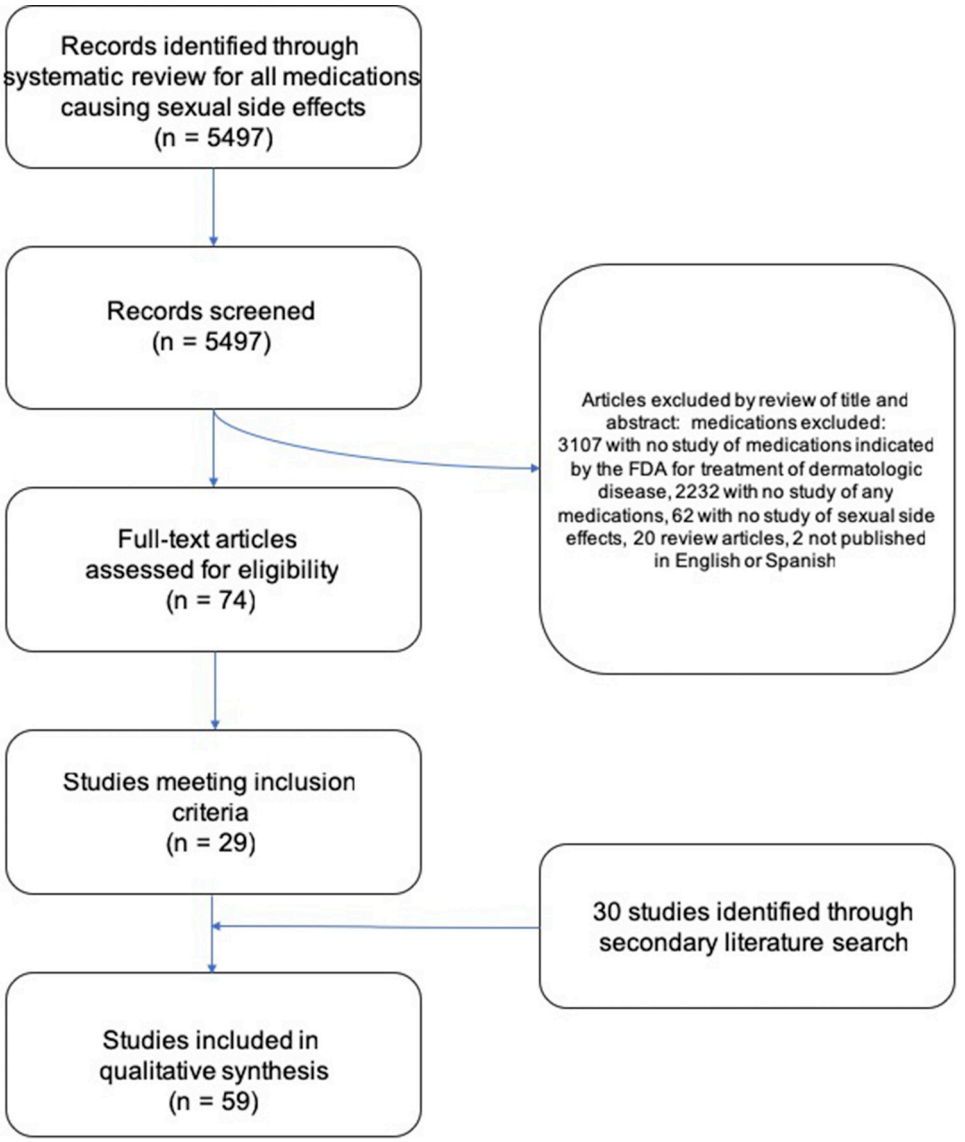

Fig 1. Systematic review of the literature for medications with United States Food and Drug Administration (FDA)–approved dermatologic indications and evidence of adverse effects of sexual dysfunction.

Table I. Summary of systemic dermatologic medications with sexual adverse effects

Medication (dose) & adverse effect	No. of studies	Highest level of evidence study*	Sexual dysfunction reported as 1° outcome or adverse event	Lowest dose evaluated in highest level of evidence study	Sexual adverse effects described in prescribing information	Author's recommendations
Finasteride (1 mg)						
ED	13[4-16]	1b[12]	Adverse event	1 mg/d[12]	Decreased libido (1.8%), ED (1.3%), and ejaculation disorder (1.2%) based on clinical trials and sexual dysfunction that continued after discontinuation, including ED and libido, ejaculation, and orgasm disorders	Screen all patients taking finasteride for ED, decreased libido, and ejaculation disorders, even when used at the 1-mg dose. Consider discontinuation in patients experiencing these adverse effects. If discontinued, monitor patient for recovery of sexual function. Avoid concurrent NSAID use.
Ejaculation disorder	7[4,5,7,12,14,16,17]	1b[7]	1°	5 mg/d[7]		
Low libido	12†	1b[12]	Adverse event	1 mg/d[12]		
Persistent sexual dysfunction	12[4,8,10,11,17,20-26]	2b[8]	1°	≤1.25 mg/d[8]		
Itraconazole (200-400 mg/d)						
ED	2[27,28]	4[27]	Adverse event	50-400 mg/d[27]	Decreased libido and impotence occurring in 1% of patients in clinical trials and reports ED in postmarketing reports	Consider screening patients taking itraconazole and with pre-existing risk factors for ED and decreased libido. Consider treatment with fluconazole or griseofulvin in patients with risk factors for sexual dysfunction or patients undergoing treatment for sexual dysfunction.
Low libido	1[27]	4[27]	Adverse event	50-400 mg/d[27]		
Corticosteroids (5-60 equivalent mg/d prednisone)						
ED	2[29,30]	4[29]	1°	13 equivalent mg prednisone/d	Not available	Screen all patients taking corticosteroids for at least 3 months for ED and decreased libido.
Low libido	1[29]	4[29]	1°	13 equivalent mg prednisone/d		
Cyclosporine (2.5-5 mg/kg)						
ED	1[31]	3b[31]	1°	Not available	Not available	Screen all patients taking cyclosporine at the dermatologic dose, especially those with pre-existing risk factors, for sexual dysfunction, for ED only.

Methotrexate (10-25 mg/wk)						
ED	4[32-35]	4[32-34]	1°	5 mg/wk po[32,34]	Rare loss of libido/impotence	Consider screening patients taking methotrexate, especially those with pre-existing risk factors for sexual dysfunction, for ED, loss of libido, and Peyronie disease. If identified, dose reduction may be sufficient to ameliorate adeffects.
Low libido	1[34]	4[34]	1°	15-20 mg/wk po[34]		
Peyronie disease	2[36,37]	4[37]	1°	10 mg/wk po[37]		
Thalidomide (100-400 mg/d)						
ED	2[38,39]	4[38,39]	1°	50-100 mg/wk[38,39]	Decreased libido and sexual dysfunction reported as adverse effects	Screen patients taking thalidomide with pre-existing risk factors for sexual dysfunction for loss of libido. Consider screening patients taking thalidomide, especially those with pre-existing risk factor for sexual dysfunction, for premature ejaculation, and ED.
Ejaculation disorder	1[38]	4[38]	1°	100 mg/wk[38]		
Low libido	3[38,40,41]	1b[40,41]	Adverse event	100 mg/wk[40,41]		
Gabapentin (150-3600 mg/d)						
ED	2[42,43]	4[42,43]	1°	300 mg/d[42]	Changes in libido, ejaculation disorder, and anorgasmia identified in postmarketing experience	Consider screening patients taking gabapentin, especially those with pre-existing risk factors for sexual dysfunction and those taking higher daily doses, for ejaculatory dysfunction, decreased libido, ED, and anorgasmia. Dose reduction may ameliorate adverse effects.
Ejaculation disorder	1[44]	4[44]	1°	1200 mg/d[44]		
Low libido	1[45]	4[45]	1°	900 mg/d[45]		
Anorgasmia	3[42,46,47]	4[47]	1°	900-1800 mg/d		
Pregabalin (150-300 mg/d)						
ED	3[48-50]	2b[50]	1°	300 mg/d[48]	Anorgasmia reported as a frequent adverse reaction, while abnormal ejaculation reported as an infrequent reaction	Screen all patients taking pregabalin for ED and ejaculatory dysfunction. Consider screening patients taking pregabalin, especially those with pre-existing risk factors, for sexual dysfunction for anorgasmia.
Ejaculation disorder	4[48-51]	2b[50]	1°	300 mg/d[49,51]		
Anorgasmia	2[49,51]	4[49,51]	1°	300 mg/d[49,51]		

Continued

Table I. Cont'd

Medication (dose) & adverse effect	No. of studies	Highest level of evidence study*	Sexual dysfunction reported as 1° outcome or adverse event	Lowest dose evaluated in highest level of evidence study	Sexual adverse effects described in prescribing information	Author's recommendations
Isotretinoin (0.5-1.0 mg/kg/d)						
ED	1[52]	2b[52]	1°	Not available[52]	Not available	Screen all patients taking isotretinoin, especially those with pre-existing risk factors for sexual dysfunction, for ED. Consider screening patients taking isotretinoin, especially those with pre-existing risk factors for sexual dysfunction, for ejaculatory dysfunction. Dose reduction may ameliorate side effects. If patients have concurrent depressive symptoms, treatment of depression may also improve symptoms.
Ejaculation disorder	1[53]	4[53]	1°	1 mg/kg/d[53]		
Acitretin/etretinate (25-50 mg/d)						
ED	3[54-56]	4[54-56]	1°	25 mg/d[55]	Decreased libido encountered in clinical trials	Consider screening patients taking acitretin/etretinate, especially those with pre-existing risk factors for sexual dysfunction, for ED.

ED, Erectile dysfunction; *NSAID*, nonsteroidal anti-inflammatory drug; *po*, by mouth (oral); *1°*, primary.

*2009 Centre for Evidence-based Medicine Level of Evidence: 1a, systematic review of randomized controlled trials; 1b, individual randomized controlled trials; 2a, systematic review of cohort studies; 2b, individual cohort study; 3a, systematic review of case-control study; 3b, individual case-control study; 4, case series and studies.

†References [4,5,7-9,11,12,14,15,17-19].

Antifungal

Itraconazole. Itraconazole was associated with sexual adverse effects in 2 case series. One series identified 2 patients with decreased libido and 1 with impotence among 189 patients treated for a variety of indications with itraconazole (50-400 mg/d) for a median of 5 months.[27] In another series of 42 patients with paracoccidioidomycosis and histoplasmosis who were treated with itraconazole (50-100 mg/d) for 6 months, 1 patient with normal hormone levels reported impotence.[28]

Anti-inflammatory/immunomodulatory

Corticosteroids. We identified 2 studies that demonstrated sexual adverse effects in patients taking systemic corticosteroids.[29,30] In 1 observational study of 17 men taking 10 mg/d methylprednisolone, 52% reported reduced libido and 58% ED.[29] A case report of a 34-year-old man with congenital adrenal hyperplasia who began dexamethasone also described the development of impotence while taking 1 mg/d dexamethasone, with improvement of symptoms after a dose reduction to 0.5 mg/d.[30]

Cyclosporine. In a single multicenter, cross-sectional study of 809 male renal transplant patients, ED was significantly more likely to develop in those using cyclosporine than in those on other immunosuppressive regimens (78.4% vs 63.2%; $P < .001$).[31]

Methotrexate. Among both dermatologic and rheumatologic literature, ED, loss of libido, and Peyronie disease have been demonstrated to occur with methotrexate therapy.[32-37] Wylie et al[34] described 2 patients who experienced ED during treatment with 10 and 15 mg/wk methotrexate for chronic plaque psoriasis. Sexual impotence and loss of morning erections developed in a 52-year-old man with rheumatoid arthritis when he was prescribed 12.5 mg/wk methotrexate.[33] Patients prescribed 12.5 mg/wk, 7.5 mg/wk, and 5 mg/wk also reported ED, loss of morning erections, and inability to ejaculate, respectively.[32] Several reported these symptoms resolved after discontinuation and re-emerged when treatment was restarted.[32-34]

May et al[36] described a 51-year-old man with psoriasiform dermatitis who presented with erectile pain after 8 months of treatment with 20 mg/wk. His symptoms resolved after discontinuation of methotrexate but recurred after rechallenge. Ultimately, Peyronie disease developed. Phelan et al[37] similarly described the development of Peyronie disease in 2 patients with rheumatoid arthritis. The first was 48 years old, and palpable fibrous nodule and curvature of the penis developed after 5 months of 10 mg/wk treatment that resolved after discontinuation. The second patient was 58 years old, and curvature and fibrosis developed after 6 months of treatment at 15 mg/wk. The patient had partial resolution of symptoms when methotrexate was discontinued 2 years later.

Methotrexate-related adverse effects are typically managed with folic acid supplementation; however, the efficacy of folic acid in alleviation of sexual adverse effects has not been evaluated.

Thalidomide. We identified 3 studies describing sexual adverse effects in patients taking thalidomide. The first of these studies was a double-blind clinical trial of 95 men randomized to receive a 24-week course of either placebo or 100 or 300 mg/d thalidomide tablets for the treatment of Behçet disease. Five patients taking thalidomide (2 taking 100 mg/d and 3 taking 300 mg/d) experienced loss of libido compared with none who received the placebo.[40] Similar results were observed in a double-blind, crossover study of 75 patients with aphthous stomatitis randomized to receive a 2-month course of 100 mg/d thalidomide, followed by 2 months of placebo, or the reverse. Two patients taking thalidomide experienced loss of libido compared with none in those taking the placebo.[41] Pouaha et al[38] also described development of premature ejaculation and ED in addition to loss of libido in 2 patients taking 100 mg/d thalidomide. Symptoms resolved in both patients after a dose reduction to 50 mg/d in 1 patient and 50 mg dosed on alternate days in the second.[38] Finally, in a report of 11 patients taking 50 to 100 mg/d thalidomide, ED developed in 6 patients within 4 weeks.[39]

Neurotrophic drugs

Gabapentin. We identified 3 studies that described anorgasmia related to gabapentin.[42,46,47] The first described anorgasmia with no change in libido in a 52-year-old patient treated for neuropathic pain related to a thoracotomy scar after uptitration of the gabapentin dose from 300 to 900 mg/d; symptoms resolved after a dose reduction to <900 mg/d.[46] Similarly, Brannon and Rolland[65] described the case of a 25-year-old man experiencing anorgasmia after treatment with 900 mg/d gabapentin; symptoms resolved when switched to valproic acid. Finally, in a case series of 9 elderly men treated with gabapentin, 3 experienced progressive anorgasmia.[47] Ejaculatory dysfunction,[44] decreased libido,[45] and ED[42,43] are less commonly reported adverse effects, occurring at doses >900 mg/d. Because sexual dysfunction typically occurs at higher dosage, dose reduction should be considered in any patient experiencing these symptoms.

Pregabalin. In 1 study, ED developed in 5 patients after the addition of pregabalin to their antiepileptic regimen at varying doses. ED resolved on cessation of pregabalin for the 2 patients who decided to discontinue the medication.[48] Another report described the development of delayed ejaculation and anorgasmia in a 35-year-old man treated with pregabalin (300 mg/d), which resolved upon cessation of treatment.[51] An additional report described the development of anorgasmia in 3 epileptic patients treated with pregabalin (300 mg/d).[49] Finally, the International Index for Erectile Function questionnaire was completed by 31 patients with neuropathic pain taking pregabalin, 34 patients with neuropathic pain with no treatment, and 37 age-matched controls.[50] Compared with the control group, both groups of patients with neuropathic pain had lower scores; however, those patients treated with pregabalin exhibited significantly lower scores than untreated patients with neuropathic pain.

Retinoids

Isotretinoin. Our review identified a single case study describing a 29-year-old man with a progressive inability to ejaculate within several weeks of initiating 1 mg/kg/d. The ejaculatory dysfunction resolved within 3 days of discontinuation of the medication. According to the authors' correspondence with the drug manufacturer, there were 150 reports of sexual adverse effects in men taking isotretinoin, including ejaculatory dysfunction and ED.[53] ED was described in 1 nonrandomized, prospective trial of 55 patients with refractory acne treated with isotretinoin or minocycline. A significantly higher proportion of patients taking isotretinoin had an inability to maintain an erection (30% vs 5.7%; $P < .05$). Symptoms improved after discontinuation of isotretinoin, and no difference in serum testosterone or dehydroepiandrosterone sulfate was identified between groups.[52] However, 60% of the isotretinoin group reported depressive symptoms,[52] which may be confounding the relationship between isotretinoin and ED. Moreover, these adverse effects may be dose dependent, such that dose reduction should be considered in patients presenting with sexual dysfunction.

Acitretin/etretinate. One report described development of ED in a 40-year-old man without laboratory abnormalities or depressive symptoms after treatment with 50 to 75 mg/d etretinate for generalized psoriasis. ED resolved promptly with discontinuation but developed again upon medication rechallenge.[54] Another report describes a 39-year-old man with an inability to maintain an erection during 45 consecutive days of treatment with 25 mg/d acitretin.[55] The patient denied prior sexual dysfunction, and normal erections returned within 2 weeks of stopping the drug. A third report described ED in a 37-year-old-man with ichthyosis vulgaris who received etretinate for 6 months with a total dose of 890 mg and a maintenance dose of 0.64 mg/kg/d; symptoms improved after etretinate was stopped.[56]

Limitations

Many of the included studies were limited by sample size and methodology, which precluded some evaluation of the validity of findings. Some studies reported sexual dysfunction as an adverse effect and did not include any formal evaluation of male sexual function. Furthermore, there was a large variation in number of studies evaluating male sexual function as an adverse effect to included medications. To report studies with higher levels of evidence, we gave preference to large meta-analyses and excluded their primary studies to prevent any reporting bias. Future study of this topic requires more robust evaluation through prospective randomized trials powered to explore sexual dysfunction as a primary outcome.

CONCLUSION

Sexual functioning is an important, yet often overlooked, aspect of male health that can be disrupted by commonly used dermatologic medications. We identified 11 medications with evidence of sexual adverse effects, of which level 1 evidence assessing sexual dysfunction as a primary outcome was available for finasteride. These adverse effects occur through various mechanisms, including hormonal changes, direct effects on penile smooth muscle, changes in penile tissue vasculature, and psychologic confounding factors.

Patients are often hesitant to seek help when experiencing sexual dysfunction[66] and may not suspect medications to be the underlying cause of their symptoms. Therefore, it is crucial for the prescribing dermatologist to be aware of the potential for sexual dysfunction with these medications and encourage an open dialogue with patients regarding their sexual health. Specific recommendations for screening for sexual adverse effects are described in Table I. In general, we recommend actively screening all patients taking medications with at least level 3 evidence of sexual adverse effects occurring in patients taking the dermatologic dose. We recommend screening all patients with pre-existing risk factors for sexual dysfunction, such as smoking, obesity, dyslipidemia, diabetes, older age, hypertension, or

other comorbidities,[2] who are taking medications with evidence of sexual effects at higher doses or with level 4 evidence of sexual adverse effects at the dermatologic doses. In the event patients experience sexual dysfunction taking these medications, relief may be achieved by lowering the dose or switching to an alternative agent. The information in this review may serve as a reference of adverse effects when deciding on a therapeutic agent and a guide to help identify patients who should be screened for sexual dysfunction.

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