

Culprits of Medication-Induced Telogen Effluvium, Part 1

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PRACTICE POINTS

- Medications are a common culprit of telogen effluvium (TE), and medication-induced TE should be suspected in patients presenting with diffuse nonscarring alopecia who are taking systemic medication(s).
- A careful history of new medications and dose adjustments 1 to 6 months prior to notable hair loss may identify the most likely inciting cause.
- Medication-induced TE often improves with cessation or dose reduction of the culprit medication.

Telogen effluvium (TE) is a common clinical consequence of medication-related alopecia. The inciting cause of TE may be difficult to identify due to delays in clinically apparent hair loss. Because medication-induced TE is a nonscarring alopecia that typically is reversible, appropriate management requires identification of the underlying triggering medication and cessation of it, if possible. In part 1 of this series, we review the existing literature on medication-induced TE with a focus on systemic retinoids, antifungal agents, and psychotropic medications.

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Alopecia is a commonly reported side effect of various medications. Anagen effluvium and telogen effluvium (TE) are considered the most common

mechanisms underlying medication-related hair loss. Anagen effluvium is associated with chemotherapeutic agents and radiation therapy, with anagen shedding typically occurring within 2 weeks of medication administration.^{1,2} Medication-induced TE is a diffuse nonscarring alopecia that is a reversible reactive process.³⁻⁵ Telogen effluvium is clinically apparent as a generalized shedding of scalp hair 1 to 6 months after an inciting cause.⁶ The underlying cause of TE may be multifactorial and difficult to identify given the delay between the trigger and the onset of clinically apparent hair loss. Other known triggers of TE include acute illness,^{7,8} nutritional deficiencies,^{4,9} and/or major surgery.¹⁰

Each hair follicle independently and sequentially progresses through anagen growth, catagen transition, and telogen resting phases. In the human scalp, the telogen phase typically lasts 3 months, at the end of which the telogen hair is extruded from the scalp. Anagen and telogen follicles typically account for an average of 90% and 10% of follicles on the human scalp, respectively.¹¹ Immediate anagen release is hypothesized to be the mechanism underlying medication-induced TE.¹² This theory suggests that an increased percentage of anagen follicles prematurely enter the telogen phase, with a notable increase in hair shedding at the conclusion of the telogen phase approximately 1 to 6 months later.¹² First-line management of medication-induced TE is identification and cessation of the causative agent, if possible. Notable regrowth of hair is expected several months after removal

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of the inciting medication. In part 1 of this 2-part series, we review the existing literature to identify common culprits of medication-induced TE, including retinoids, antifungals, and psychotropic medications.

Retinoids

Retinoids are vitamin A derivatives used in the treatment of a myriad of dermatologic and nondermatologic conditions.^{13,14} Retinoids modulate sebum production,¹⁵ keratinocyte proliferation,¹⁶ and epithelial differentiation through signal transduction downstream of the ligand-activated nuclear retinoic acid receptors and retinoid X receptors.^{13,14,17} The recommended daily dosage of retinol is 900 µg retinol activity equivalent (3000 IU) for men and 700 µg retinol activity equivalent (2333 IU) for women. Retinoids are used in the treatment of acne vulgaris,¹⁸ psoriasis,¹⁹ and ichthyosis.²⁰ The most commonly reported adverse effects of systemic retinoid therapy include cheilitis, alopecia, and xerosis.²¹ Retinoid-associated alopecia is dose and duration dependent.^{19,21-24} A prospective study of acitretin therapy in plaque psoriasis reported that more than 63% (42/66) of patients on 50 mg or more of acitretin daily for 6 months or longer experienced alopecia that reversed with discontinuation.²³ A systematic review of isotretinoin use in acne showed alopecia was seen in 3.2% (18/565) of patients on less than 0.5 mg/kg/d of isotretinoin and in 5.7% (192/3375) of patients on 0.5 mg/kg/d or less of isotretinoin.²⁴ In a phase 2 clinical trial of orally administered 9-*cis*-retinoic acid (alitretinoin) in the treatment of Kaposi sarcoma related to AIDS, 42% (24/57) of adult male patients receiving 60, 100, or 140 mg/m² alitretinoin daily (median treatment duration, 15.1 weeks) reported alopecia as an adverse effect of treatment.²⁵ In one case report, a patient who ingested 500,000 IU of vitamin A daily for 4 months and then 100,000 IU monthly for 6 months experienced diffusely increased shedding of scalp hair along with muscle soreness, nail dystrophy, diffuse skin rash, and refractory ascites; he was found to have severe liver damage secondary to hypervitaminosis A that required liver transplantation.²⁶ Regarding the pathomechanism of retinoid-induced alopecia, animal and in vitro studies similarly have demonstrated that all-*trans*-retinoic acid appears to exert its inhibitory effects on hair follicle growth via the influence of the transforming growth factor β2 and SMAD2/3 pathway influence on dermal papillae cells.^{14,27} Development of hair loss secondary to systemic retinoid therapy may be managed with dose reduction or cessation.

Antifungals

Azole medications have broad-spectrum fungistatic activity against a wide range of yeast and filamentous fungi. Azoles inhibit sterol 14α-demethylase activity, impairing ergosterol synthesis and thereby disrupting plasma membrane synthesis and activity of membrane-bound enzymes.²⁸ Fluconazole is a systemic oral agent in this

class that was first approved by the US Food and Drug Administration (FDA) for use in the 1990s.²⁹ A retrospective study by the National Institute of Allergy and Infectious Disease Mycoses Study Group followed the clinical course of 33 patients who developed alopecia while receiving fluconazole therapy for various mycoses.³⁰ The majority (88% [29/33]) of patients received 400 mg or more of fluconazole daily. The median time to hair loss after starting fluconazole was 3 months, and the scalp was involved in all cases. In 97% (32/33) of patients, resolution of alopecia was noted following discontinuation of fluconazole or a dose reduction of 50% or more. In 85% (28/33) of patients, complete resolution of alopecia occurred within 6 months of fluconazole cessation or dose reduction.³⁰ Fluconazole-induced TE was reproducible in an animal model using Wistar rats³¹; however, further studies are required to clarify the molecular pathways of its effect on hair growth.

Voriconazole is an azole approved for the treatment of invasive aspergillosis, candidemia, and fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species. A retrospective survey study of patients who received voriconazole for 1 month or longer found a considerable proportion of patients developed diffuse reversible hair loss.³² Scalp alopecia was noted in 79% (120/152) of patients who completed the survey, with a mean (SD) time to alopecia of 75 (54) days after initiation of voriconazole. Notable regrowth was reported in 69% (79/114) of patients who discontinued voriconazole for at least 3 months. A subgroup of 32 patients were changed to itraconazole or posaconazole, and hair loss stopped in 84% (27/32) with regrowth noted in 69% (22/32) of patients.³² Voriconazole and fluconazole share structural similarity not present with other triazoles.^{33,34} Because voriconazole-associated alopecia was reversed in the majority of patients who switched to itraconazole or posaconazole, the authors hypothesized that structural similarity of fluconazole and voriconazole may underlie the greater risk for TE that is not a class effect of azole medications.³¹

Psychotropic Medications

Various psychotropic medications have been associated with hair loss. Valproic acid (or sodium valproate) is an anticonvulsant and mood-stabilizing agent used for the treatment of seizures, bipolar disorder (BD), migraines, and neuropathic pain.^{35,36} Divalproex sodium (or divalproex) is an enteric-coated formulation of sodium valproate and valproic acid with similar indications. Valproate is a notorious culprit of medication-induced hair loss, with alopecia listed among the most common adverse reactions (reported >5%) on its structure product labeling document.³⁷ A systemic review and meta-analysis by Wang et al³⁸ estimated the overall incidence of valproate-related alopecia to be 11% (95% CI, 0.08-0.13). Although this meta-analysis did not find an association between incidence of alopecia and dose or duration of

valproate therapy,³⁸ a separate review suggested that valproate-induced alopecia is dose dependent and can be managed with dose reduction.³⁹ A 12-month, randomized, double-blind study of treatment of BD with divalproex (valproate derivative), lithium, or placebo (2:1:1 ratio) showed a significantly higher frequency of alopecia in the divalproex group compared with placebo (16% [30/187] vs 6% [6/94]; $P=.03$).⁴⁰ Valproate-related hair loss is characteristically diffuse and nonscarring, often noted 3 to 6 months following initiation of valproate.^{41,42} The proposed mechanism of valproate-induced alopecia includes chelation of zinc and selenium,⁴³ and a reduction in serum biotinidase activity, thereby decreasing the availability of these essential micronutrients required for hair growth.⁴¹ Studies examining the effects of valproate administration and serum biotinidase activity in patients have yielded conflicting results.⁴⁴⁻⁴⁶ In a study of children with seizures including 57 patients treated with valproic acid, 17 treated with carbamazepine, and 75 age- and sex-matched healthy controls, the authors found no significant differences in serum biotinidase enzyme activity across the 3 groups.⁴⁴ In contrast, a study of 75 children with seizures on valproic acid therapy stratified by dose (mean [SD])—group A: 28.7 [8.5] mg/kg/d; group B: 41.6 [4.9] mg/kg/d; group C: 64.5 [5.8] mg/kg/d—found that patients receiving higher doses (groups B and C) had significantly reduced serum biotinidase activity (1.22 [1.11] and 0.97 [0.07] mmol/min/L, respectively) compared with 50 healthy pediatric controls (5.20 [0.90] mmol/min/L; $P<.001$). The same study found biotin supplementation at 10 mg/d for 20 days led to resolution of alopecia in 22% (2/9) of patients with alopecia on valproic acid therapy.⁴⁵ Despite hypothesized effects of valproate on micronutrients, the role of mineral supplementation in treating valproate-associated hair loss remains unclear. There is evidence to suggest that valproic acid-associated alterations in serum biotinidase activity may be transient. In a study of 32 pediatric patients receiving valproic acid for the treatment of epilepsy, serum biotinidase activity was significantly lower after 3 months of valproic acid therapy compared with pretreatment levels ($P<.05$); at 6 months, the serum biotinidase activity was increased compared with 3 months ($P<.05$) and not significantly different from pretreatment levels ($P>.05$).⁴⁶ Hair regrowth has been observed following discontinuation or dose reduction of valproate therapy in some cases.^{39,47}

Lithium carbonate (lithium) is used in the treatment of BD. Despite its efficacy and low cost, its potential for adverse effects, narrow therapeutic index, and subsequent need for routine monitoring are factors that limit its use.⁴⁸ Some reported dermatologic adverse reactions on its structure product labeling include xerosis, thinning of hair, alopecia, xerosis cutis, psoriasis onset/exacerbation, and generalized pruritus.⁴⁹ A systematic review and meta-analysis of 385 studies identified 24 publications reporting adverse effects of lithium on hair with no significantly increased risk of alopecia

overall.⁵⁰ The analysis included 2 randomized controlled trials comparing the effects of lithium and placebo on hair loss in patients with BD. Hair loss was reported in 7% (7/94) of patients taking lithium and 6% (6/94) of the placebo group in the 12-month study⁴⁰ and in 3% (1/32) of the lithium group and 0% (0/28) of the divalproex group in the 20-month study.⁵¹ Despite anecdotal reports of alopecia associated with lithium, there is a lack of high-quality evidence to support this claim. Of note, hypothyroidism is a known complication of lithium use, and serum testing of thyroid function at 6-month intervals is recommended for patients on lithium treatment.⁵² Because thyroid abnormalities can cause alopecia distinct from TE, new-onset alopecia during lithium use should prompt serum testing of thyroid function. The development of hypothyroidism secondary to lithium is not a direct contraindication to its use⁵³; rather, treatment should be focused on correction with thyroid replacement therapy (eg, supplementation with thyroxine).⁵⁴

Commonly prescribed antidepressant medications include selective serotonin reuptake inhibitors (SSRIs) and bupropion. Selective serotonin reuptake inhibitors affect the neuronal serotonin transporter, increasing the concentration of serotonin in the synaptic cleft available for stimulation of postsynaptic serotonin receptors^{55,56}; bupropion is an antidepressant medication that inhibits norepinephrine and dopamine reuptake at the synaptic cleft.⁵⁷ Alopecia is an infrequent (1 in 100 to 1 in 1000 patients) adverse effect for several SSRIs.⁵⁸⁻⁶² A recent systematic review identified a total of 71 cases of alopecia associated with SSRI use including citalopram ($n=11$), escitalopram ($n=7$), fluoxetine ($n=27$), fluvoxamine ($n=5$), paroxetine ($n=4$), and sertraline ($n=20$), with a median time to onset of hair shedding of 8.6 weeks (range, 3 days to 5 years). Discontinuation of the suspected culprit SSRI led to improvement and/or resolution in 63% (51/81) episodes of alopecia, with a median time to improvement and/or resolution of 4 weeks.⁶³ A comparative retrospective cohort study using a large US health claims database from 2006 to 2014 included more than 1 million new and mutually exclusive patients taking fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram, paroxetine, duloxetine, venlafaxine, desvenlafaxine, and bupropion.⁶⁴ Overall, 1% (1569/150,404) of patients treated with bupropion received 1 or more physician visits for alopecia. Patients on SSRIs generally had a lower risk for hair loss compared with patients using bupropion (citalopram: hazard ratio [HR], 0.80 [95% CI, 0.74-0.86]; escitalopram: HR, 0.79 [95% CI, 0.74-0.86]; fluoxetine: HR, 0.68 [95% CI, 0.63-0.74]; paroxetine: HR, 0.68 [95% CI, 0.62-0.74]; sertraline: HR, 0.74 [95% CI, 0.69-0.79]), with the exception of fluvoxamine (HR, 0.93 [95% CI, 0.64-1.37]). However, the type of alopecia, time to onset, and time to resolution were not reported, making it difficult to assess whether the reported hair loss was consistent with medication-induced TE. Additionally, the authors acknowledged

that bupropion may have been prescribed for smoking cessation, which may carry a different risk profile for the development of alopecia.⁶⁴ Several other case reports have described alopecia following treatment with SSRIs, including sertraline,⁶⁵ fluvoxamine,⁶⁶ paroxetine,⁶⁷ fluoxetine,⁶⁸ and escitalopram.⁶⁹

Overall, it appears that the use of SSRIs portends relatively low risk for alopecia and medication-induced TE. Little is known regarding the molecular effects of SSRIs on hair growth and the pathomechanism of SSRI-induced TE. The potential benefits of discontinuing a suspected culprit medication should be carefully weighed against the risks of medication cessation, and consideration should be given to alternative medications in the same class that also may be associated with TE. In patients requiring antidepressant therapy with suspected medication-induced TE, consider transitioning to a different class of medication with lower risk of medication-induced alopecia; for example, discontinuing bupropion in favor of an SSRI.

Final Thoughts

Medication-induced alopecia is an undesired side effect of many commonly used drugs and drug classes, including retinoids,azole antifungals, and mood stabilizers. Although the precise pathomechanisms of medication-induced TE remain unclear, the recommended management often requires identification of the likely causative agent and its discontinuation, if possible. Suspicion for medication-induced TE should prompt a thorough history of recent changes to medications, risk factors for nutritional deficiencies, underlying illnesses, and recent surgical procedures. Underlying nutritional, electrolyte, and/or metabolic disturbances should be corrected. In part 2 of this series, we will discuss medication-induced alopecia associated with anticoagulant and antihypertensive medications.

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