# Emerging Unconventional Therapies for Alopecia Areata

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**Alopecia areata is a prevalent autoimmune skin disease with no cure or indicated treatment options. In the absence of an approved treatment, some patients are eager to try unconventional therapies, despite the very limited research evaluating their safety and efficacy. Recently emerging unconventional therapies for alopecia areata discussed include antihistamines, cryotherapy, and low-dose naltrexone.**

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Alopecia areata (AA) is an autoimmune disease that results in the loss of hair on the scalp and elsewhere on the body. Despite recent advancements in understanding the pathology of this disease, there remain no approved treatment options. AA is a chronic condition that is highly unpredictable and the disease course is different for each person, ranging from a few patches to complete loss of hair on affected areas. Hair can spontaneously regrow, or fall out again at any time. AA can cause significant psychological and social challenges for patients and their families. Depression, anxiety, and suicidal ideation are health issues that can accompany AA.

Current AA treatment methods are of limited effectiveness and are more successful in treating less extensive forms of the disease. Commonly used therapies include intralesional corticosteroid injections in areas of hair loss, which are limited by pain and cost of frequent office visits, and topical immunotherapies, which can have prohibitive irritant and allergic side effects. Promising new treatment options, such as JAK inhibitors, have systemic immunomodulating effects, are costly, and not currently approved for use in AA.

In an attempt to better control their disease, patients with AA often seek alternative and somewhat unconventional therapies. The internet search engine results yield a plethora of promising products, many obtained without medical advice, whereas others require prescription or a visit with a physician. Alternative treatments that have recently gained popularity among patients with AA include antihistamines, cryotherapy, and low-dose naltrexone (LDN). These unconventional AA remedies pose a challenge for patients and physicians alike, as they are not part of the standard AA therapeutic repertoire. In addition, there is inadequate data evaluating their efficacy and even safety in AA. Available evidence about the mechanisms of these treatment options points to a potential, but unproven, role in AA.

## Antihistamines

Atopic dermatitis is the most common comorbidity of AA, affecting an estimated half of patients. Some patients with AA experience episodes of hair loss alongside flares of their atopic disease. Furthermore, histologic evaluations of the affected scalp demonstrate proinflammatory mast cells adjacent to hair follicles in AA. These mast cells are secretors of histamine and are thought to facilitate crosstalk with CD8+ T cells, contributing to collapse of the follicular immune privilege observed in AA (Bertolini et al., 2014).

In AA, antihistamines have been primarily used as an adjunct to topical diphenylcyclopropenone therapy, aimed to reduce the severity of concomitant side effects. The enhancement of hair growth in those instances has been classically attributed to diphenylcyclopropenone. However, several authors have described that antihistamines can enhance hair regrowth on their own, including a case of a patient with ophiasis, who after failing prior therapies, responded to administration of fexofenadine 120 mg/d (Nonomura et al., 2012; Soltanahmadi and Akhyani, 2012). Fexofenadine is a histamine H1 receptor antagonist with a relatively safe profile and no marked sedation. It has been shown to decrease the production of IFN-γ from T lymphocytes and expression of ICAM-1 on epithelial cells. Possible ways by which antihistamines such as fexofenadine work include decreased IFN-γ production, decreased expression of ICAM-1 on epithelial cells, and inhibited IL-4-induced expression of IL-5. This suggests that patients who have atopic dermatitis and AA may benefit from antihistamines, but controlled clinical trials are needed to confirm this relationship.

## Cryotherapy

Cryotherapy devices are readily accessible in dermatological offices where the typical patient with AA will seek help. The potential mechanism by which cryotherapy modulates hair regrowth appears to be of immune-regulatory nature. Cryotherapy and hypothermia have been associated with reduced in vitro and in vivo T-cell and monocyte activation response, reduced IL-17 release in T cells, reduced IL-1β/IL-23 activation of T cells, and reduced granzyme B (Lindsay et al., 2016). Several studies have assessed the efficacy of cryotherapy in the treatment of AA. A study comparing cryotherapy and clobetasol propionate lotion in patchy recalcitrant AA showed response rates of 80% and 91.5% hair regrowth in respective treatment groups (Faghihi and Radan, 2014). Complete recovery of hair growth (>95%) was not accomplished in any of the patients.

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In another study, cryotherapy was found to be inferior to injections of intralesional triamcinolone. Regrowth of more than 50% was seen in 23.3% of patients with AA treated with cryotherapy in comparison with 56.7% of patients treated with intralesional triamcinolone (Amirnia et al., 2015).

The cryotherapy technique used in the treatment of AA is not well described in the literature. In most articles, it appears that the entire area of hair loss is treated with a light spray jet every 2 weeks. In the largest study with 353 patients, there were 60.9% responders, and no severe side effects were documented, concluding that cryotherapy is an effective and safe therapeutic modality for AA (Jun et al., 2017).

**Low-dose naltrexone**

Naltrexone is an opiate antagonist used to treat addiction to heroin, morphine, and alcohol, typically at doses of 50–300 mg daily. LDN at doses of 1–4.5 mg daily emerged as an anti-inflammatory treatment in the 1980s. Since then, it has been evaluated in several small studies for the treatment of inflammatory conditions. LDN is thought to work through modulation of inflammatory mediators and upregulation of endogenous opioid receptors. Opioid peptides affect immune cytokine and chemokine signaling, and can function as immunomodulatory molecules as they have the ability to regulate T lymphocyte proliferation and block release of proinflammatory cytokines: IL-6 and IL-12, tumor necrosis factor-α, and nuclear factor NF-κB (Zagon et al., 2011).

There are several studies indicating that LDN is effective for active Crohn's disease in both adult and pediatric populations (Smith et al., 2013).

With regard to any role of LDN in the treatment of alopecia, there is not a single study describing its use in AA. The only studies in alopecia were performed in trichotillomania, where LDN-treated patients did not have any observable differences in hair loss (Grant et al., 2014).

Although the research body on LDN in alopecia is minimal, both patients and prescribers are using it. Because the presumed mechanism is anti-inflammatory, LDN can be potentially useful in inflammatory stages of AA and other alopecias. It is important to note that naltrexone, even at low dose, may hypersensitize patients to exogenous opioids. Prescribing physicians should carefully screen for potential drug interaction in patients on concurrent pain medications.

The information on emerging unconventional therapies for AA should be interpreted and utilized with a sense of caution. Clinical studies are needed to better understand their mechanisms and potential role for AA.

## CONFLICT OF INTEREST

The author states no conflict of interest.

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