



# A comprehensive review of present therapies of acanthosis nigricans

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## Original Article

### Abstract

**BACKGROUND:** Acanthosis nigricans (AN), marked by velvety skin plaques, signifies an underlying systemic disorder linked to rising obesity and diabetes rates. This study explores a comprehensive investigation of current AN treatment options, aiding clinicians in choosing effective and appropriate interventions for patients.

**METHODS:** A literature review was conducted using databases such as Google Scholar, PubMed, and MEDLINE, focusing on AN treatments in the last decade and totally 32 articles were evaluated.

**RESULTS:** Topical treatments, including retinoids, vitamin D analogs, keratolytics, and peels, are explored. Topical retinoids, especially tretinoin and adapalene, have demonstrated efficacy in clinical studies, while vitamin D analogs like calcipotriol show promise. Systemic treatments, such as oral retinoids (isotretinoin, acitretin, etretinate), insulin sensitizers (metformin, rosiglitazone), and other oral medications, are discussed. Metformin stands out for its effectiveness in treating AN associated with insulin resistance (IR). Cosmetic lasers, including alexandrite and carbon dioxide (CO<sub>2</sub>) lasers, offer successful outcomes in treating AN although cost and availability can be limiting factors. Other treatments, such as podophyllin, fish oil, photochemotherapy (PUVA), and surgery, are also considered.

**CONCLUSION:** AN necessitates a multifaceted approach, targeting both underlying systemic disorders and cosmetic concerns. The findings underscore the significance of topical treatments, systemic therapies like metformin, and the promising role of cosmetic lasers in AN management. Despite limitations in available studies, this comprehensive overview provides valuable insights for healthcare providers, emphasizing the need for personalized treatment strategies. As the prevalence of AN rises globally, continued research and clinical exploration are essential to refine and expand treatment options for this dermatological condition.

**KEYWORDS:** Acanthosis Nigricans; Insulin Resistance; Diabetes Mellitus

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## Introduction

Acanthosis nigricans (AN) is a dermatological condition marked by symmetrical, thickened, velvety, brown-to-black plaques on the skin. AN typically presents as an indicator of an underlying systemic disorder, often linked to insulin resistance (IR), diabetes mellitus (DM), obesity, internal malignancies, endocrine disorders, and reactions to drugs.

Hyperpigmented plaques can appear on any part of the body, most frequently observed in skin folds and creases, on the back and sides of the neck, axilla, groin, and external genitalia.<sup>1,2</sup> Malignant AN usually develops swiftly and severely, often in association with malignancies or congenital glandular disorders, whereas benign AN has a slower onset and affects a smaller area of the body.<sup>3</sup>

The prevalence of AN is increasing due to the rise in obesity and DM rates among the population. In one study, researchers discovered AN in 39% of the obese children in

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their study sample.<sup>4</sup> Prevalence ranges from 7% to 74% based on age, race, AN type, obesity, and endocrine issues, with higher occurrences in native and African Americans.<sup>5</sup>

Several pathophysiological factors are associated with IR at the skin. Insulin-like growth factor (IGF), fibroblast growth factor receptor (FGFR), and epidermal growth factor receptor (EGFR) have been identified as drivers of epidermal keratinocyte and dermal fibroblast proliferation. These factors contribute to both the pro-inflammatory state and abnormal glucose and lipid metabolism pathways, potentially leading to AN development.<sup>6,7</sup>

The treatment of AN should always target the correction of the underlying disease.<sup>8</sup> There is no agreed-upon best treatment for AN. However, treating the skin lesions is essential due to cosmetic concerns, even though they are not inherently dangerous.<sup>9</sup>

Correction of hyperinsulinemia can lessen AN lesions, while weight loss may resolve hyperkeratotic lesions in obesity-related cases.<sup>9</sup> Diet, exercise, and behavioral changes are key treatments. In drug-induced AN, discontinuing the causative drug and using an alternative treatment can lead to resolution. For malignancy-associated AN, surgical tumor removal is the main treatment.<sup>7,10</sup>

Treatment options for AN have not been widely researched, but smaller clinical trials and case reports in the literature can guide healthcare providers in devising treatment strategies. This review seeks to provide readers with a comprehensive look at current AN treatment options with the aim of assisting clinicians in selecting the most effective and suitable treatment for patients.

## Methods

**Database:** A literature review of AN was conducted by searching English-published articles in Google Scholar, PubMed, and MEDLINE databases.

**Selection:** The focus was on AN treatment,

specifically on studies published within the last 10 years although all available articles were reviewed from 1984 to 2023. Additional articles were identified by examining the references of the reviewed sources selected for inclusion. Priority was given to articles and case reports that centered on AN and its treatment. Finally, 32 articles were evaluated. The keywords used for the search included “acanthosis nigricans”, “topical treatment”, “systemic treatment”, and “cosmetic laser”.

**Analysis:** The analysis method employed in this study was content analysis, which allows the readers to provide a comprehensive and nuanced overview of current available AN treatments by categorizing and synthesizing the information extracted from the literature.

## Results

### Topical treatments

**Topical retinoids:** Topical retinoids are the primary treatment, especially when no underlying disease process is detectable. They normalize epidermal turnover, correct hyperkeratosis, and restore epidermal thickness to its normal state.<sup>5</sup> In a study conducted in India, after 14 days of applying 0.05% tretinoin, all 30 patients with treatment-resistant AN displayed clinical improvement. By the 16-week mark, 80% of these patients (24 individuals) achieved complete clearance. Yet, to sustain these positive effects, intermittent tretinoin application was necessary, as relapses occurred within 4 weeks after discontinuation of treatment.<sup>11</sup> From a histopathological perspective, the characteristic alterations of hyperkeratosis and the accumulation of keratotic material between papillae were no longer observed in the biopsy after 8 weeks of tretinoin application.

Two case reports demonstrated the efficacy of topical 0.1% tretinoin in improving AN. In the first case, an 18-year-old woman achieved clearance of her neck AN within 10 days. Within 2 weeks, her axillae showed improved

color and reduced hyperkeratosis.<sup>12</sup> In the second case, a patient applied tretinoin 0.1% gel twice daily for 2 weeks, resulting in the clearance of AN in the left axilla. Conversely, the untreated right axilla showed no improvement.<sup>13</sup>

Adapalene gel's effectiveness in treating childhood AN was the focus of two studies. In Thailand, a randomized controlled trial (RCT) involved 16 children who applied 0.1% adapalene to one side of their AN-affected neck, resulting in minimized skin darkening. The therapeutic effect was attributed to changes in epidermal keratinization, and it was notably well-tolerated without significant skin irritation.<sup>14</sup> In a separate study conducted in India, a split-site comparison involved 16 pediatric patients with AN treated with 0.1% adapalene gel. This study revealed a  $60.7 \pm 28.5\%$  improvement in the mean skin color ratio. The therapeutic side displayed significant improvement, demonstrated by a decrease in the mean skin color ratio compared to the untreated side at weeks 2 and 4.<sup>15</sup> Adapalene is available without a prescription and is notable for causing less irritation compared to other retinoid derivatives.<sup>15</sup>

In 2019, a split-neck comparative RCT revealed that 0.1% adapalene gel and 0.025% tretinoin cream demonstrated similar efficacy in treating childhood AN lesions.<sup>16</sup> Another randomized comparative clinical trial conducted by Treerichod et al. revealed that 0.025% tretinoin cream, when compared to 10% urea, led to a more significant improvement in AN treatment. It is noteworthy that both treatments significantly reduced neck hyperpigmentation among the patients.<sup>17</sup>

In an individual case report, an 11-year-old boy dealing with morbid obesity and AN experienced positive results with topical tazarotene 0.05% cream. Notably, tazarotene cream stands out due to its lower likelihood of causing burning, stinging, and irritation, promoting better patient compliance.<sup>18</sup>

Combination therapies offer promising avenues for AN treatment. In a case involving obesity-related AN, the use of both 0.05% tretinoin cream and 12% ammonium lactate cream led to resolution.<sup>19</sup> Additionally, in a case of idiopathic AN, a nightly application of a depigmenting cream containing 0.05% tretinoin, 4% hydroquinone, and 0.01% fluocinolone acetonide, coupled with daily sunscreen use, demonstrated positive results within a month.<sup>20</sup>

**Topical vitamin D analogs:** Another option for topical treatment of AN are vitamin D analogs. Calcipotriol is a common vitamin D analogue utilized for various dermatoses and it works by inhibiting keratinocyte proliferation and promoting differentiation through molecules such as involucrin and transglutaminase-1 (TGM1).<sup>21</sup> This is achieved through increased intracellular calcium and cyclic guanosine monophosphate (GMP) levels.<sup>5</sup> Additionally, it reduces the cutaneous effects of insulin by limiting the number of active keratinocytes available for targeting.<sup>22</sup> In the literature, there are reports highlighting the efficacy of calcipotriol in treating AN. One instance involved a 60-year-old obese man with mixed-type AN in flexural areas, showing improvement after applying 0.005% calcipotriol cream twice daily for 3 months.<sup>23</sup> Similarly, a case featured an obese woman with AN lesion, which improved with the application of calcipotriol ointment twice daily over the same duration.<sup>24</sup> In another report, two cases of umbilical nevoid AN showed favorable clearance after three weeks of treatment with topical calcipotriol.<sup>25</sup> Notably, Gregoriou et al. emphasized calcipotriol's safety, effectiveness, and good tolerance as a treatment option for AN, especially when addressing the underlying cause is not attainable.<sup>26</sup>

**Keratolytics:** Lactic acid, an alpha-hydroxy acid (AHA), functions as a peeling agent and induces the disintegration of desmosomes by releasing desmogleins.<sup>1</sup> Despite the evidence

supporting the positive impact of using the combination of 12% ammonium lactate with 0.05% tretinoin in improving AN lesions, a case series study demonstrated that this effect was less compared to alexandrite laser.<sup>19,27</sup>

Another option is topical urea cream. A recent double-blind study in 2022 revealed that urea cream could effectively reduce AN hyperpigmentation in adolescents. Specifically, the 20% concentration showed better efficacy compared to the 10% concentration.<sup>28</sup> The efficacy of 10% urea cream compared to topical 10% salicylic acid in treating AN was examined in another randomized comparative study. As a result, both drugs led to the improvement of hyperpigmentation caused by AN, and this therapeutic effect was similar for both.<sup>29</sup> Unlike salicylic acid, patients using urea in this trial did not report any cutaneous irritation. A two-month usage of 10% urea cream decreased the thickness and darkness of the AN plaques in a case report of Crouzon syndrome with AN; however, the results were considered as unfavorable.

**Peels:** Trichloroacetic acid (TCA) is a superficial chemical exfoliating agent that functions by inducing epidermal destruction, followed by repair and rejuvenation. TCA, particularly in a 15% concentration, exhibits caustic properties, resulting in protein coagulation and subsequent frosting. The precipitation of proteins triggers epidermal necrosis and destruction, leading to inflammation and the activation of wound repair mechanisms. Ultimately, this process facilitates re-epithelialization and the replacement of smoother and less pigmented skin.<sup>5</sup> TCA possesses multiple advantages in terms of safety, accessibility, cost-effectiveness, and ease of preparation. Additionally, its stability and predictable characteristics, such as precipitation, absorption, and peel depth, simplify the assessment of the endpoint for exfoliation.<sup>7</sup> In a pilot study conducted by Zayed et al., six female patients with AN

demonstrated improvement following the use of TCA peels. The observed improvements included reductions in hyperpigmentation, thickening, and an overall enhancement in the skin's appearance.<sup>30</sup> Another study evaluating the effects of glycolic acid peel and fractional carbon dioxide (CO<sub>2</sub>) laser on AN therapy was carried out by Zaki et al. The side that received the glycolic acid peel exhibited greater clinical improvement after three sessions (43% vs. 19%).<sup>31</sup> Furthermore, no side effects have been reported as a result of glycolic acid usage.

### Systemic treatments

**Oral retinoids:** Oral retinoids, such as isotretinoin, acitretin, and etretinate, have been employed as treatment options for AN. Nevertheless, these therapies are accompanied by significant drawbacks, including the requirement for high dosages, prolonged treatment durations, potential teratogenic consequences, and a risk of relapse upon discontinuation of therapy.<sup>32,33</sup> Cell growth, differentiation, morphogenesis, and cohesiveness are all impacted by retinoid compounds in different ways. It has been hypothesized that the normalization of epithelial growth and differentiation is the mechanism of action.<sup>7,34</sup>

In a 1980 report, Katz documented the clearance of obesity-associated AN with isotretinoin at a dose of 3 mg/kg/day. However, lesions relapsed upon treatment cessation, underscoring the importance of maintenance therapy. Notably, the treatment did not impact the underlying endocrinologic abnormality.<sup>35</sup> Another case highlighted the sustained improvement of AN lesions through a combination of isotretinoin and metformin.<sup>36</sup> Isotretinoin also proved effective in resolving AN lesions associated with nodulocystic acne in a patient with Costello syndrome and in a case of paraneoplastic AN linked to gastric adenocarcinoma after retinoid treatment.<sup>37,38</sup>

Acitretin has been used to treat AN barely, and has shown inconsistent outcomes. An



18-year-old man with generalized idiopathic AN experienced complete recovery after 45 days of acitretin treatment at a dosage of 0.8 mg/kg (50 mg), divided into two daily doses. However, upon starting maintenance therapy with 25 mg of acitretin daily for 2 months, lesions recurred. The recurrence was later resolved through the topical application of 0.1% retinoic acid.<sup>39</sup> A child with generalized AN received treatment with acitretin, starting at 0.6 mg/kg for a week and subsequently increasing to 1 mg/kg for an additional 14 days. This was coupled with the use of emollient and keratolytic creams, but the ultimate outcome was unsatisfactory.<sup>40</sup> Acitretin is not a suitable option for adolescent girls due to the potential for long-term teratogenic effects, which can persist up to 3 years after discontinuation of the medication.<sup>41</sup>

A 20-year-old woman with generalized benign hereditary AN achieved rapid and recurrence-free clearance with etretinate at a dosage of 1 mg/kg/day.<sup>42</sup> Another case with generalized lipodystrophy (Lawrence-Seip syndrome) achieved AN clearance with etretinate at 75 mg/day, maintained at 50 mg/day for several months.<sup>43</sup> In a prior report, a breast cancer patient with AN did not experience effective outcomes following treatment with etretinate, but this outcome may have resulted from the underlying factor's persistence in this case.<sup>44</sup>

*Metformin and rosiglitazone:* Insulin sensitizers, such as metformin, are beneficial in treating IR obesity-related AN (IRORAN).<sup>22</sup> Metformin is a type of biguanide which lowers glucose production by increasing insulin sensitivity, resulting in reduced hyperinsulinemia, body weight, and fat mass.<sup>5,45</sup> Metformin, in addition to controlling glucose profiles, acts as an anti-inflammatory agent for DM-associated skin disorders like AN.<sup>46</sup> It inhibits nuclear factor kappa B (NF- $\kappa$ B), reduces hyperandrogenemia [especially in polycystic ovary syndrome

(PCOS)], and offers potential antioxidant protection.<sup>47</sup> A recent clinical trial was conducted on 60 patients with AN and IR. 40 patients were treated with 500 mg metformin three times daily and 20 control patients received placebo for three months. Those treated with metformin showed clinically significant improvement in AN on the neck and axilla, though not in AN on the knuckles, fingers, or elbows.<sup>10</sup> In a case series of three obese adolescents with IRORAN resistant to topical therapy, including calcipotriol and corticosteroids, metformin (ranging from 850 mg once daily to 850 mg twice daily) and dietary modifications were administered. Subjective improvements in IRORAN were noted without adverse reactions, and no relapses occurred after one year.<sup>48</sup> In a case of IRORAN, a 14-year-old boy underwent metformin treatment at 850 mg twice daily. Despite the treatment, the AN did not exhibit any resolution after 6 months, and the patient's weight increased.<sup>49</sup> Rosiglitazone is also helpful in the treatment of AN associated with IR.<sup>8</sup> Bellot-Rojas et al. carried out a randomized comparative trial comparing metformin (500 mg three times daily) and rosiglitazone (4 mg once daily) in 27 obese adults with AN over 12 weeks.<sup>50</sup> Although rosiglitazone resulted in lower fasting insulin levels, both agents showed only minimal improvement in skin texture. The metformin group reported adverse effects of nausea, flatulence, and diarrhea, while the rosiglitazone group experienced headaches. In a study with 5 participants (2 adolescents and 3 adults), metformin treatment for 6 months resulted in decreased body weight, IR, and insulin secretion. AN subjectively improved in both adolescents and one adult.<sup>51</sup> After eight years on metformin, a boy with normal weight and AN, coupled with IR, experienced complete clearance.<sup>52</sup> This implies that prolonging metformin treatment might be crucial for observing clinical changes in the skin. In proof

of this, an adolescent with IR and AN was cleared of AN after two years on metformin.<sup>43</sup>

**Other oral medications:** Combination therapy with metformin and thiazolidinediones (TZDs) has been observed to be advantageous in patients with AN, as TZDs help to increase insulin.<sup>53</sup> In a case report, a 48-year-old woman with DM-associated AN demonstrated improvement in her AN lesions after 2 years of use by adding sitagliptin and pioglitazone to insulin therapy.<sup>54</sup>

Alpha-lipoic acid (ALA) is a novel potent antioxidant and insulin sensitizer which is effective in reducing blood glucose levels. Its combination with biotin, zinc sulfate, and calcium pantothenate exhibits efficacy comparable to metformin in treating AN, as demonstrated in an RCT with 33 patients.<sup>55</sup>

An obese boy with AN underwent treatment with subcutaneous octreotide, a somatostatin analogue, at a dosage of 50 µg thrice daily for 5 months. The results showed improvement in AN, reduction in body weight, and decreased IR, persisting six months after the treatment was stopped.<sup>56</sup>

Combining metformin and oral contraceptives is a treatment option for individuals with hyperandrogenemia, IR, and AN (HAIR-AN syndrome).<sup>1,57</sup>

In a 2017 open pilot trial, significant weight reduction and improvement in AN lesions in the axilla and neck was observed after 12 weeks of melatonin treatment at a dosage of 3 mg/day.<sup>58</sup> Enhancement of IR and reduction of inflammation might be the potential mechanisms of action.<sup>58</sup>

**Cosmetic lasers:** To date, several cosmetic lasers have been proposed for the treatment of AN.<sup>7</sup> The alexandrite laser, for example, induces tissue remodeling and pigment decline by aiming at melanin in hair and inducing thermal healing of the skin. In a case report by Rosenbach and Ram, more than 95% improvement in axillary AN was reported after seven sessions of long-pulse alexandrite

laser (5 msec) with no recurrence during the follow-up.<sup>59</sup> Slight discomfort during sessions and a few minor superficial ulcers were the side effects. Long-pulsed alexandrite laser exhibited a greater reduction in pigmentation of axillary AN compared to a combination of topical tretinoin and ammonium lactate.<sup>27</sup> Due to the possibility of post-inflammatory hyperpigmentation, people with darker skin tones might not consider this laser to be a good option.<sup>7</sup>

The CO<sub>2</sub> laser is a further laser option for treating AN. In a recent randomized-controlled split study conducted in 2023, 23 patients with AN underwent treatment with fractional CO<sub>2</sub> laser and Q-switched laser during 4 months. The results showed an effective improvement of AN by using both of the lasers with no significant difference.<sup>60</sup> The possible mechanism is transepidermal elimination of dermal content, which helps reduce skin thickness and texture by removing melanin.<sup>60,61</sup> In a case of cervical cancer with AN of the lips, it was noted that after treatment with CO<sub>2</sub> laser, most lip plaques were debulking.<sup>7,62</sup> In a comparative study conducted in 2021, twenty cases with neck-AN were subjected to treatment using both retinoic acid (5%) peel and fractional-ablative CO<sub>2</sub> laser. The results indicated that the CO<sub>2</sub> laser treatment was more effective in addressing neck-AN.<sup>63</sup>

Fractional 1550-nm erbium fiber laser was found to be more effective for reduction of hyperpigmentation and roughness of AN with fewer adverse effects when compared it to 0.05% tretinoin cream.<sup>64</sup> This suggests a promising new and safe treatment method for AN, which requires further investigation.

**Other treatments:** It has been reported that using a 20% solution of podophyllin in alcohol can temporarily resolve AN lesions on the hands. However, due to severe local reactions and the regrowth of warty lesions, it is considered a less favorable choice.<sup>65</sup>

Fish oil is a compound containing omega-3

fatty acids.<sup>66</sup> One patient with AN and a lipodystrophic form of DM experienced improvements in skin texture and hyperpigmentation after 6 months of treatment with fish oil.<sup>67</sup>

An elderly patient with malignant AN was treated with systemic photochemotherapy (PUVA) over nine weeks, resulting in complete relief of pruritus and significant regression of pigmented keratoses and intertriginous maceration.<sup>68</sup>

In rare cases, surgical therapy of the AN lesions may be attempted if conservative approaches prove ineffective, especially in malignant AN associated with carcinoma.<sup>69</sup>

## Discussion

AN is not a standalone disease but rather a sign of various underlying causes. It is not treated directly as a separate condition. Although the primary objective of therapy is to address the underlying cause, achieving cosmetic resolution of AN lesions is crucial for improving patients' quality of life.<sup>8,70</sup> Because underlying disease is often associated with skin conditions, treatment for AN is diverse.

When assessing AN for the first time, IR syndrome – which is marked by obesity, dyslipidemia, hypertension (HTN), and type II DM – must be taken into consideration.<sup>5</sup> A comprehensive assessment should be performed by clinicians, which should include a fasting glucose, insulin and lipid panel, complete blood count (CBC), and liver function tests. Imaging investigations such as computed tomography (CT)/magnetic resonance imaging (MRI) and plain radiography may provide useful information if malignancy-associated AN is suspected.<sup>5</sup>

In a cosmetic approach, topical retinoids are used as the first line of treatment for AN lesions, and although they have shown good therapeutic effects, due to the potential for recurrence, they may require repeated treatment courses.<sup>11</sup> In studies conducted on

the treatment of AN in children, adapalene gel has demonstrated significant therapeutic effects and safety, making it a favorable option for AN treatment in children.<sup>14,15</sup> Another option is the use of topical tazarotene cream, which, due to its milder irritation and burning sensations, may offer better tolerance, although its effects have not been extensively studied yet.<sup>18</sup> Combination therapies of topical retinoids with other medications have shown positive results; however, further investigations are needed to determine their effects and potential side effects more conclusively.<sup>19,20</sup>

Vitamin D analogs such as calcipotriol have been reported as an effective and safe topical treatment, particularly when treating the root cause is not possible.<sup>23,24,26</sup> For nevoid AN, the usage of this cream has demonstrated outstanding results in less than a month of treatment.<sup>25</sup>

Other topical treatments include keratolytics like urea, lactic acid, and salicylic acid, which can be used to improve hyperpigmentation in AN lesions.<sup>1,29</sup> Among these, a 20% urea cream has shown more effective performance compared to 10%, making it a preferable topical treatment for adolescents.<sup>28</sup>

The reduction of hyperpigmentation and skin thickness are among the benefits of using peels such as TCA and glycolic acid, which make them accessible alternatives to topical creams.<sup>30,31</sup>

Oral retinoids are one of the main systemic medications for treating AN, with isotretinoin showing more positive evidence in the treatment of AN among them.<sup>35,37,38</sup> Oral retinoids, due to their high required doses, long treatment durations, and the potential for lesion recurrence, come with limitations for prescribing as a treatment for AN.<sup>32,33</sup> The available evidence regarding acitretin is limited and contradictory, but it appears that this medication carries a high risk of recurrence, and along with it, there is a perceived need for supplementary

treatment.<sup>39,40</sup> It appears that the use of tretinoin can lead to a rapid and non-recurrent resolution of AN lesions,<sup>42,43</sup> although these effects require confirmation through clinical trial investigation.

Since one of the main causes of AN is DM and IR, insulin sensitizer drugs such as metformin, especially when used for an extended period, play a significant role in improving these skin lesions.<sup>22</sup> The impact of these drugs on AN lesions has been reported to be more significant in the neck and axilla areas compared to other regions of the body.<sup>10</sup> These effects are more noticeable when accompanied by dietary modifications and are associated with a lower possibility of recurrence.<sup>48</sup> Additionally, encouraging outcomes have been seen when metformin is used in combination with other medications including isotretinoin and TZDs.<sup>36,53</sup> In cases where AN lesions result from IR with symptoms of hyperandrogenism or signs of PCOS, a combination therapy of metformin with oral contraceptive pills (OCP) can be beneficial.<sup>1,57</sup>

Other systemic treatments such as somatostatin analogs, melatonin, and ALA have also been suggested for the treatment of IR-associated AN (IRAN) and could be considered as alternative options.<sup>55,56,58</sup>

When it comes to treating AN lesions, cosmetic lasers such as the CO<sub>2</sub> and alexandrite lasers have created remarkably successful results.<sup>59,60</sup> The alexandrite laser was the first laser suggested for the treatment of AN.<sup>59</sup> Despite greater therapeutic results as compared to topical tretinoin,<sup>27</sup> it has several downsides, including discomfort feeling during therapy, mild superficial injuries, and post-inflammatory hyperpigmentation.<sup>7,27</sup> The latest laser technologies, such as CO<sub>2</sub> lasers and Q-switched lasers, have been the focus of recent studies for treating AN, and the outcomes from these investigations have been notably positive.<sup>60</sup> Among the challenges with these lasers are their low cost-benefit value

and lack of general availability.

Other available treatments include podophyllin, fish oil, PUVA, and dermabrasion, which can be considered alongside primary treatments.<sup>65,67-69</sup>

In general, after initial assessments to determine the underlying disease and setting up the necessary steps for diagnosis and treatment, specific dermatologic interventions can be pursued, especially in cases with severe skin lesions and based on the patient's cosmetic preferences.

Among the limitations of this study, it is worth mentioning the limited number of articles and the scarcity of trial studies on this topic. Given these limitations, it is recommended that future trial studies be designed and conducted with the aim of a more detailed examination of the effects, side effects, and recurrence of AN treatment methods, with a larger sample size.

## Conclusion

The most crucial principle for treating AN is the identification and treatment of the underlying causative factors like DM. Besides, there are various options available for the cosmetic treatment of AN. This review offers a comprehensive overview of the current landscape of AN treatments, providing healthcare providers with a detailed knowledge of the options available. Topical treatments such as retinoids and calcipotriol are relatively affordable and effective options. In cases of AN associated with IR and obesity, oral insulin sensitizers such as metformin can be utilized. Recent findings suggest promising prospects for the use of various cosmetic lasers with significant efficacy in treating AN, indicating a potentially increased utilization in the future. At this point, no treatment can be believed superior to others, and the decision to choose each one depends on the specific conditions of each patient, made in consultation with a clinician.



### Conflict of Interests

Authors have no conflict of interests.

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