Received: 1 November 2020 | Revised: 8 February 2021 | Accepted: 22 February 2021

DOI: 10.1111/dth.14915

REVIEW ARTICLE

DERMATOLOGIC THERAPY WILEY

# A systematic review of N-acetylcysteine for treatment of acne vulgaris and acne-related associations and consequences: Focus on clinical studies

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## Abstract

Acne vulgaris is one of the most common dermatologic disorders affects people of all races and ethnicities and has many adverse effects on the quality of life. The increased bacterial resistance to antibiotics has reduced the effectiveness of treatment with these agents. There is an increasing focus on the involvement of oxidative stress in the pathophysiology of acne. This study investigates the effect of N-acetylcysteine (NAC) as an antioxidant in the treatment of acne vulgaris. This systematic review was conducted through a search in databases such as Science Direct, PubMed, Scielo, and Medline using keywords including acne vulgaris, anti and NAC, and all the keywords associated with each of the subtitles. The factors affecting the occurrence and expansion of acne include increased sebum synthesis, hyperkeratinization of pilosebaceous units, colonization with *Propionibacterium acnes*, and increased release of inflammatory mediators and ROS. Studies have shown that glutathione stimulation following the administration of NAC increases glutathione levels for the detoxification of oxygen-free radicals. Moreover, NAC prevents the synthesis and release of inflammatory cytokines such as TNF-α, IL-8, IL-6, MP9, and IL-1β and has shown antibacterial activities against important bacteria including *E. coli*, *S. epidermidis*, *Pseudomonas*, and *Klebsiella*. This medication has antiproliferative effects and is also used for excoriation and PCOD. The results of the present study showed the beneficial effects of using NAC in patients with acne vulgaris in terms of the disease complications and comorbidities. Given its diverse functional mechanisms, this medication can be used to treat acne and its consequences.

**KEYWORDS**
acne, acne scar, anti-bacterial, anti-hyperkeratinization, anti-inflammatory, excoriated acne, excoriation, N-acetylcysteine, polycystic ovary disease, systemic review antioxidant

## 1 | INTRODUCTION

As a prevalent disease in adolescents and adults[1,2] and one of the 10 most prevalent disorders in the world,[3] acne affects over 80% of adolescents and the young.

Although it is not life-threatening, the psychosocial impact of acne includes adverse impact on multiple dimensions of quality of life, including effects on self-perception, socialization, emotional health and occupational opportunities, and may be associated with anxiety and depressive symptoms, as well as body dissatisfaction.[4]

  

The destructive effects of acne on QoL are resemble those of certainchronic diseases including diabetes and coronary artery diseases.[5]

Given the need for long-term poly-therapies and their side effects, which sometimes require changes in treatment regimens, the patients usually fail to completely adhere to the medications.[6]

The burden of medical expenses associated with this prevalent disease has not been accurately calculated; nevertheless, calculating the work or school time lost by the patients and their parents and the costs of prescription medication indicated that huge costs are imposed on the healthcare system and community.[7,8]

The damage to pregnant and breastfeeding women caused by the majority of these treatments can also cause treatment interruption.[9]

Available treatments for acne are limited in type rather than cost, and these methods have remained unchanged for decades. Proposing modern and safe therapeutic methods with fewer complication scan therefore significantly improve the health status and quality of life in the patients.[10]

Acne is treated according to its clinical form and the pathophysiological mechanisms involved in it.[10]

N-acetylcysteine (NAC) is a common antidote for acetaminophen intoxication. This medication has generally been used as a mucolytic agent.[11]

N-acetylcysteine is a thiol-containing compound that is a synthetic derivative of N-acetyl from the androgenic amino acid L.cysteine (a precursor to glutathione antioxidant enzyme).[12] The stimulation of glutathione synthesis following the administration of NAC increases the amount of glutathione for the detoxification of oxygen-free radicals. Many studies have shown that NAC prevents the production and release of the inflammatory cytokines like TNF-α, IL-8, IL-6, MP9, and IL-1β. NAC has also shown antibacterial activities against important bacteria including *E. coli*, *S. epidermidis*, *Pseudomonas*, and *Klebsiella*.[13]

NAC is used in oral, topical, and IV forms.[14] This medication has an unpleasant taste and odor and should therefore be used with fruit juice.[15] It is normally safe when used orally at a dose of 2400 mg or less per day.[16] At this dosage, its side-effects are mild and include nausea and vomiting, flushes, epigastric pain, constipation, and skin rash. Hives, skin rash, headache, fever, and shivering may be seen at higher doses.[15]

This medication is administered in various medical fields, including neurology, nephrology, psychiatry, and pulmonary. For example, it has been administered as adjuvant therapy for Alzheimer's, contrast-induced nephropathy, HIV, COPD, eradication of *H. pylori*, IPD, etc.[17,18]

NAC has been used for dermatological purposes in trials and case reports and is a safe option for the treatment of skin disorders. It has been effective as an adjuvant for TEN, trichotillomania, ichthyosis, dermatitis, melasma, alopecia, connective tissue diseases, skin picking, excoriated acne, and protection against photo-aging skin damage.[19,20] The effectiveness of oral and topical NAC has been assessed in a few studies and the medication has been shown to help improve inflammatory acne lesions by reducing ROS, inhibiting leukotrienes and prostaglandin, stabilizing membranes, and inhibiting lipidperoxidation.[21]

Given the studies conducted on the applications and effectiveness of NAC on acne and its complications, including excoriated acne, as well as its functional mechanisms and potential anti-fibrotic effects, which may be able to moderate another side-effect of acne, namely scarring, the present review study was carried out on the applications of NAC in treating acne and its side-effects, since this multipotent medication seems to be able to find a special place, especially as a complementary therapy, in controlling acne.

## 2 | MATERIALS AND METHODS

All the relevant articles published from 2000 to 2020 (April 15) were searched for writing this review article. The search encompassed the effect of NAC on acne and its side-effects and comorbidities, and all the relevant clinical studies were classified in separate subtitles. The present review was conducted through a search in databases including Science Direct, PubMed, Scielo, and Medline and using the keywords "acne vulgaris", "antioxidant", and "N-acetylcysteine","acne", and "NAC."

## 3 | DISCUSSION

Acne is a chronic inflammatory disease of the pilosebaceous unit.[21,22] It appears in areas with many sebaceous glands, such as the face, the chest and the back.[23-25] In most cases, it is a self-limiting complaint. However, it takes several years for acne to naturally resolve in this patient group,[25] and it imposes a considerable burden on those affected by the disease[26-28] as it has been linked to depression, anxiety,[21] low self-esteem,[29,30] and diminished quality of life independent of duration, severity of acne or age.[28,30,31] Moreover, acne lesions can evolve into more permanent scars and postinflammatory hyperpigmentation,[21,23] in up to 43% of the patients, especially in those with prolonged uncontrolled acne,[32] and early treatment is thus encouraged.[33]

An effective acne treatment often involves using several medications to target two or more of the four pathogenic mechanisms associated with acne.[23,24,26,33,34]

The factors affecting the occurrence and spread of acne include increased sebum synthesis, hyperkeratinization of the pilosebaceous units, colonization with *Propionibacterium acnes* and increased release of inflammatory mediators and ROS.[35]

Acne is initiated with changes in the quality (dyssebacia) and quantity (hyper-secretion) of lipid-rich sebum due to androgenstimulation.[22-24,36] This lipid-rich environment helps the follicular development of *P. acnes* and *P. acnes* biofilm formation. *P. acnes* then hydrolyzes the sebum lipid releasing unsaturated fatty acids capable of inducing hyperkeratinization of the follicular epithelium,[37,38] leading to the obstruction of the follicles and the subsequent micro-comedones formation.[22,38,39] The micro-

comedones can then progress to noninflammatory comedones or inflammatory lesions such as papules, pustules, nodules, and cysts.[23]

Acne is treated according to its severity, the patient's skin type, clinical category, and the presence of skin scars.[40]

Treatments include appropriate skin care topical medication (retinoids, antimicrobial, azelaic acid and salicylic acid, BPO, Dapsone) and Oral medications (antibiotics, contraceptives, anti-androgen agents, isotretinoin).For some people, the following therapies might be helpful, either alone or in combination with medications (light therapy, chemical peel, drainage and extraction, steroid injection).[41,42]

These methods are often used in combination and can be modified and changed if required. The type of combination therapies used and their side-effects, bacterial resistance, high costs, treatment limitations in pregnant and lactating women, and possible contraindications of the medications (underlying diseases and medication interactions, etc.) have led to the failure of the available treatments.[40,43-45]

None of the available treatments is considered a definitive treatment for acne, since they cause major side-effects.

## 3.1 | N-acetylcysteine

N-acetylcysteine is a thiol-containing compound and a source of cysteine that basically acts as a strong antioxidant but has numerous functional mechanisms.

## 3.2 | 1-Antioxidant

There has been a particular interest in recent years in the amount of oxidative stress involved in acne pathogenesis. Emerging studies have shown that patients with acne are exposed to increased skin and systemic oxidative stress.[46,47]

Propionibacterium seems to have an important initiating role in the pathogenesis of acne inflammation by producing low-molecular-weight chemotactic factors,[48] which leads to the accumulation of neutrophils at the site of acne comedones.

The attracted neutrophils, after phagocytosis, release inflammatory factors, such as lysosomal enzymes, with resultant damage to the follicular epithelium.[49,50]

The role of reactive oxygen species generated by neutrophils in the mediation of tissue injury has been studied recently. Reactive oxygen species generated by activated neutrophils have been reported to be capable of causing tissue injury, called auto-oxidative damage, at the sites of inflammation.[51-53] These oxidants can attack DNA or membrane lipids, or both, resulting in a chemical insult to the surrounding healthy tissue. Reactive oxygen species generated by neutrophils are closely correlated with the pathogenesis of a variety of inflammatory skin diseases.[54,55]

Akamatsu et al[56] revealed that the level of neutrophil-produced hydrogen peroxide increases significantly in patients with acne inflammation compared to patients with acne comedones and healthy controls. No significant difference was observed between the patients with acne comedones and the healthy controls.

To quench these reactive oxygen species, the cell has enzymes such as glutathione peroxidase, catalase and superoxide dismutase and sulf-hydryl compounds, of which glutathione is the most important. Glutathione consists of glutamate, glycine and cysteine, and the last amino acid limits its synthesis in times of stress.[57]

N-acetylcysteine is a thiol-containing compound and an acetylated derivative of the amino acid L. cysteine, and as aprecursor to glutathionen-acetylcysteine has also been shown to scavenge reactive oxygen species directly.[58]

## 3.3 | Anti-inflammatory action

Inflammatory acne is the result of the host's response to *Propionibacterium acnes* in the follicles (natural flora with no invasive and serious infection).[59]

*Propionibacterium acnes* exhibit complex interactions with key events in the acne pathogenesis. This bacterium interacts with innateimmunity, including toll-like receptors, antimicrobial peptides, and metalloproteinase matrix, and increases the secretion of inflammatory cytokines, including IL-6, IL-1B, IL-8, IL-12, IL-1a, TNF-a, and GM-CSF by keratinocytes, sebocytes and macrophages.[60,61]

N-acetylcysteine has been shown to decrease the levels of IL-6 in patients on hemodialysis.[62] TNF-$\alpha$ and IL-1$\beta$ have also been shown to decrease in mice models treated with NAC.[63]

N-acetylcysteine inhibits the activation of redox-sensitive nuclear factor-kappa B, which stimulates the expression of pro-inflammatory genes in times of oxidative stress, leading to release of a large amount of inflammatory cytokines.[64]

## 3.4 | Anti-proliferative effects

In the normal follicle, the keratinocytes are shed as single cells to the lumen and then excreted. In acne, keratinocytes hyperproliferate and are not shed as normal. They also become densely packed along withmonofilaments and lipid droplets. Comedogenesis occurs when abnormally desquamated corneocytes accumulate in the sebaceous follicle.[24]

N-acetylcysteine has been shown to exert an inhibitory effect on NIH3T3 fibroblast cells of mice by reversibly blocking the early or mid G1 phase of the cell cycle. This makes n-acetylcysteine a potential drug for preventing and reversing fibrosis.[65] It also inhibits proliferation of human keratinocyte and has found utility in hyperproliferative diseases.[66]

The effect is due to the anti-proliferative effects of n-acetylcysteine which diminishes the hyperkeratosis of lamellar

ichthyosis and improves the skin barrier function.[67] The first article that showed improvements in lamellar ichthyosis with topical NAC was conductedon a 33-year-old woman in 1999,[66] and in another report from Turkey, the clinical effectiveness of NAC 10% emulsion in the topical treatment of congenital ichthyosis in infants was concurrently compared with the effectiveness of urea 4% emulsion. After treating the skin on the left and right halves of the body with topical NAC and urea 4% for 9 days, respectively, improvements on the left side was greater than on the right side, and complete recovery from eclabium and ectropion was reached within 16 days of treatment.[15] Moreover, a similar recovery was observed in five patients by the administration of NAC 10% and urea 5% cream for 4 months.[67] Deffenbacher also reported the recovery of an infant with congenital ichthyosis with the administration of NAC.[68]

### 3.5 | Antimicrobial effect

The microbiology of the pilosebaceous unit involves three coexisting groups of microorganisms: Gram-positive, coagulase-negative cocci (staphylococci and micrococci); anaerobic diphtheroids (*Propionibacterium acnes* and *Propionibacterium granulosum*); and lipophilic yeasts (*Pityrosporum* species). The microflora of comedones is qualitatively identical to that of the normal sebaceous follicle.

The staphylococci and micrococci are aerobes; therefore, their site of growth within the sebaceous unit is superficial, and these organisms are unable to reside in the anaerobic conditions of the infra-infundibulum where the inflammatory reaction occurs in acne. The lipophilic yeasts do not seem to play an important role in any disease conditions.[69]

*Propionibacterium acnes* is a Gram-positive and anaerobic pathogen colonized in sebaceous follicles. In general, it is more prevalent in skin areas with high sebaceous follicle density, since these follicles produce large amounts of sebum that provide a lipid-rich anaerobic environment conducive to *P. acnes*.[70]

According to McInturff and Kim,[71] *P. acnes* produces a lipase that metabolizes the sebum triglycerides to glycerol and fatty acids, which in turn may help the formation of comedones and their induced inflammation.

For over 40 years, the colonization of *P. acnes* in patients with acne vulgaris has been treated with topical or oral antibiotics,[72] thus leading to the increased prevalence of antibiotic-resistant *P. acnes* strains.[73,74]

In addition, *P. acnes*' ability to grow in a biofilm[75-78] can protect it from the host's defenses[79,80] and make it more resistant to antimicrobial medications,[77] which creates the need for more effective new antimicrobial treatments that are not resistant to bacteria.

Biofilms are responsible for acute and chronic events in infections of the airways. The difficulty of eradicating biofilms with oral antibiotics has encouraged physicians to use nonantibiotic therapies. In-vitro studies have shown the potential role of NAC as an antibiofilm agent. Indeed, there are reports on NAC's antimicrobial activity against various microorganisms and there have been suggestions of its role in various stages of biofilm formation (adhesion to surfaces, synthesis and organization of the matrix and dispersion of biofilms). NAC's ability to disrupt the formation of biofilms was first demonstrated in 1997 by Penez-Giraldo, who investigated the effect of different concentrations of NAC on bacterial development and the formation of biofilms in an *S. epidermidis* culture medium in their study and reported a concentration-dependent reduction in biofilms as well as the inhibitory effect of 2 mg of NAC on matrix formation. Since then, many studies have shown the effect of NAC on the reduction of biofilms due to microorganisms (Gram-negative and Gram-positive and yeasts) and its ability to weaken the matrix structure and biofilms. The antimicrobial activity of NAC is associated with: (a) The competitive inhibition of the use of cysteine, (b) The reaction of NAC's sulfhydryl group with bacterial proteins, and (c) Disruption in the balance of intracellular redox through a potential indirect effect on cell metabolism and signal transmission pathways.[81]

In a study conducted in Seoul in 2018, Young assessed the antibacterial effect of NAC against endodontic biofilms, including *Lactobacillus*, *Enterococcus*, and *Streptococcus mutans* on 27 dental blocks and concluded that NAC has greater effects in eradicating biofilms than other therapies (chlorhexidine).[82]

In a study in 2012 in Singapore, Samantha investigated the antibacterial and biofilm eradication effects of NAC on *Enterococcus* and found that NAC had the strongest bactericidal properties at pH = 11 and eradicated the *Enterococcus* biofilm and it was therefore found to be a bactericidal against biofilm and planktonic forms of *Enterococcus*.[83]

### 3.6 | Neurotransmission modulation

Cysteine dimerizes to form cystine which is transported across neurons via the cystine-glutamate antiporter and increases the inhibitory glutamate.[84] In addition, NAC has been shown to cause dopamine level change in neurons.[85]

### 3.7 | N-acetylcysteine and excoriation disorder

Excoriation disorder is identified with frequent and compulsory skin picking that leads to tissue damage. It affects 4% of the general population and can significantly affect the patient's QoL. It can even cause potentially life-threatening complications. For example, tissue damage due to removal can lead to topical infection and septicemia.[86]

The role of glutamatergic agents in skin picking has recently been investigated in open-label and controlled trials. Many studies have emphasized the role of glutamate dysfunction in the physiopathology of compulsive disorders. Glutamate is an excitatory neurotransmitter.[87]

These effects are due to the antioxidant and glutamate modulatory effects of NAC.

Grant et al[88] investigated skin picking disorder treatment with NAC in a randomized double-blind placebo-controlled trial on 66 patients (35 patients underwent NAC therapy and 31 acted as controls). Over 12 weeks, 1200-3000 mg of NAC or placebo were administered to the patients. The desire for skin picking reduced significantly and the therapy was well-tolerated in the intervention group. Meanwhile, no significant improvement was observed in QoL or psychosocial functioning in the cases, which may have been due to the small sample size and short follow-up period.

Another clinical trial was conducted by Miller & Angulo on 35 patients with Prader-Willi syndrome and SPD comorbidity, who received 450-1200 mg/day of NAC over 12 weeks. Skinpicking behavior improved in all the patients and 25 cases (71%) showed complete resolution of skin-picking.[89]

## 3.8 | N-acetylcysteine and acne

While N-acetylcysteine helps improve inflammatory lesions of acne by quenching reactive oxygen species, inhibition of leukotrienes and prostaglandins, stabilization of membranes and inhibiting lipid peroxidation,[90] its effect on comedones has been described as very poor, which can be due to reduced sebum or inhibition of oval Pityrosporum (a potential comedogenic organism that has been detected in comedones).[91] A single-blind randomized study conducted in Iraq showed a significant reduction in the number of inflammatory lesions in 14 patients treated with 1200 mg of NAC compared to the placebo group.[90] Another double-blind study showed a significant reduction in the number of comedones in a group of 65 patients receiving NAC 5% gel over 8 weeks compared to the control group (34 patients).[91]

## 3.9 | N-acetylcysteine and PCOS

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy that affects 5% to 20% of women of reproductive age.[92]

This disorder is usually associated with insulin resistance and infertility. Its clinical manifestations include irregular menstruation due to anovulation and skin sequel from hyperandrogenism, including hirsutism, acne vulgaris, and androgenic alopecia. The prevalence of acne has been estimated as 10% to 34% in women with PCOS.[93-96]

Nonetheless, in postpubertal and adolescent PCOS women, it is not clear whether secondary acne is caused by increased androgens or natural puberty. Acne is commonplace during puberty and is due to increased adrenal androgens with adrenarche. Moderate to severe acne has been reported in over 50% of young girls.[97]

Androgens have a role in the onset and persistence of acne.[98,99]

In acne patients, the excessive production of sebum is mainly due to the differences in the response of androgen receptor (AR) of the sebaceous glands to the circulating androgens.[24,99,100] The androgen/AR interaction causes an increase in lipid synthesis, the proliferation of the sebocytes, and inflammation.[99,101]

The effect of NAC on PCOS has been suggested in the form of low insulin secretion and improvement in hormonal profile disruption in patients. In one study, 100 patients received 1800 mg of metformin or NAC over 24 weeks. NAC had a comparable effect to metformin and reduced free testosterone and the hirsutism score 6 months after the treatment. NAC also significantly reduced LDL and Total Chol.[102] Although NAC has been used in many studies on PCOS and hyperandrogenism patients, a meta-analysis of eight clinical trials showed no significant improvement in acne and hirsutism with the administration of NAC compared to placebo.[103]

Herein Tables 1-3, classify the effect of NAC, respectively, on excoriation, acne and features of PCODs. References 104–119 are only in tables not in text.

## 3.10 | Acne scar and N-acetylcysteine

Acne scar is a cosmetic problem that may affect 95%of patients with acne and has a negative effect on QoLin young adults.[120,121]

Eighty to 90% of acne scars are atrophic, and a minority are hypertrophic and keloid.[122]

Acne scars are the result of a change in the wound healing response to cutaneous inflammation and there is infiltration of the inflammatory cells in 77% of atrophic scars.[123]

In patients not prone to scar, primary lesions have a large nonspecific immune response that subsides in resolving lesions.[124]

In contrast, in acne-prone patients, primary lesions are identified with a smaller number of CD4+ in the skin in comparison with non-scarring patients, which becomes more activated in resolving lesions.[124,125]

There is still no standard treatment for treating acne scars. To date, different treatment options have been proposed with variable outcomes and clinical complications.[126]

The potentially known systemicanti-fibrosis effects[127-129] and wound healing properties of NAC are attributed to its function as an antioxidant, nitric oxide system support, cell proliferation stimulation, migration and expression of matrix metalloproteinase collagen.[130]

Experimental studies mostly conducted on animals have reported that N-acetyl cysteine is effective in different kinds of ulcers, such as burns,[131] cut ulcers[132] and postradiotherapy ulcers.[133]

A recent study reported on the healing properties of topical N-acetyl cysteine on ulcers in two patients with nonhealing pressure ulcers.[130]

Patients with bullous morphea ulcers were subjected to treatment with N-acetyl cysteine and topical wound caring.[134]

According to the above findings regarding n-acetyl cysteine, it seems that NAC can potentially be effective in treating deep acne ulcers and its consequences, including scars, and can therefore be beneficial and effective in wound-healing processes and fibrosis

**TABLE 1** Evidences about the effect of NAC on excoriation and excoriated disorders

| | NAC and excoration | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Study** | **Study ID** | **Design** | **Duration of treatment** | **Treatment arms** | **Number of patients** | **Conclusion** |
| 105 | Glutamatergic dysfunction in skin-picking disorder treatment of a pediatric patient with n-acetylcysteine[1] | Percinel and Yazici (2014) | Case report | 10 weeks | 600-1800 mg/d NAC | A 12-year-old girl | Her SPD improved completely after 10 weeks of NAC treatment |
| 88 | N-acetylcysteine in the treatment of excoriation disorder[2] | Grant et al. (2016) | Randomized controlled trial | 12 weeks | 1200-3000 mg/day | 66 | 47% of the patients showed much or very much improved nail-biting behavior compared to 19% in the placebo group |
| 89 | An open-label pilot study of N-acetylcysteine for skin-picking in Prader-Willi syndrome | Miller and Angulo (2014) | Open-label pilot study | 12 weeks | 450-1200 mg/day | 35 | 100% of the patients showed improvement in skin-picking behaviors |

**TABLE 2** Evidences about the effect of NAC in treatment of acne

| NAC and acne | | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Study ID** | **Design** | **Number of patients** | **Treatment arms** | **Duration of treatment** | **Conclusion(s)** |
| Effects of silymarin, N-acetylcysteine and selenium in the treatment of papulopustular acne[105] | Haidar Hamid Al-Anbari (2012) | Randomized, single-blind, prospective, placebo-controlled trial | 56 (14-30 years old) | Group 1:14 patients, 8 male and 6 female, treated with silymarin 210 mg/day orally<br>Group 2:14 patients, 7 male and 7 female, treated with NAC 1200 mg/day orally<br>Group 3:14 patients, 8 male and 6 female, treated with selenium 200 μg/day orally<br>Group 4:14 patients, 7 male and 7 female, treated with placebo capsules (500 mg glucose powder) | 8 weeks | Administration of antioxidants silymarin, NAC and selenium (but not placebo) to patients with acne vulgaris significantly reduced serum MDA and increased serum GSH levels after 8 weeks compared to the pre-treatment value; they also significantly reduced serum IL-8 levels and the number of inflammatory lesions in patients with acne compared to placebos. In addition to clinical improvement, represented by reduction in the number of inflammatory lesions in patients with papulopustular acne. |

**TABLE 2** (Continued)

| NAC and acne | | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Study ID** | **Design** | **Number of patients** | **Treatment arms** | **Duration of treatment** | **Conclusion(s)** |
| The antioxidant effect of n-acetylcysteine and its role in the treatment of patients with acne vulgaris[90] | Haidar Hamid Al-Anbari | Placebo controlled blind study | 28 (14-30 years) | Group 1 was treated with N-acetylcysteine orally and topical moisturizing cream once daily at bedtime for 8 weeks. Group 2 was treated with placebo once daily orally and the same topical moisturizing cream | 8 weeks | Administration of N-acetylcysteine to patients with acne vulgaris (Group 1) significantly reduced serum MDA level and increased serum level of GSH after 8 weeks compared to the pre-treatment value and also reduced the number of inflammatory lesions by 21.41% and 48.91% after 4 weeks and 8 weeks, respectively, compared to the placebo. |
| Topical acne treatment with acetylcysteine: clinical and experimental effects[91] | Montes (2012) | Double-blind, placebo-controlled trial | 99 | Group 1 (65 patients): acetylcysteine topical gel 5%<br>Group 2: (34 patients): placebo | 8 weeks | Significantly reduced the number of comedones compared to the patients in the control group. |
| Effects of oral antioxidants on lesion counts associated with oxidative stress and inflammation in patients with papulopustular acne[90] | Ahmed Salih Sahib (2012) | Randomized prospective clinical trial | Patients (n = 56)<br>Healthy subjects (n = 28) | Group 1:14 patients, 8 male and 6 female, treated with silymarin 210 mg/day orally<br>Group 2:14 patients, 7 male and 7 female, treated with NAC 1200 mg/day orally<br>Group 3:14 patients, 8 male and 6 female, treated with selenium 200 μg/day orally<br>Group 4:14 patients, 7 male and 7 female, treated with placebo capsules (500 mg glucose powder) | 8 weeks | The administration of antioxidants to patients with acne vulgaris significantly reduced serum Malondialdehyde leveland increased the serum level of Glutathione after eight weeks compared to the pre-treatment value and also significantly reduced serumInterleukin-8 levels and the number of inflammatory lesions in patients with acne compared to the placebo. |

adjustment during the scar-formation process and also in the reduction of scar severity.

The authors of this study have been worked frequently on various aspects of acne,[135-143] and tied to introduce a multipotential drug as NAC in the field of approach to acne.

NAC has really various indications in different medical conditions due to its multi-potential properties especially its anti-oxidant anti-inflammatory immune-regulatory and many other confirmed effects even strongly proposed effects on COVID-19infection like other multi-potential drugs in this pandemic era.[144-149]

**TABLE 3** Evidences about the effect of NAC in patients with PCODs

| NAC and PCOS | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Study ID** | **Design** | **Duration of treatment** | **Treatment arms** | **Number of patients** | **Number of patients with acne (%)** | **Conclusion(s)** |
| N acetylcysteine, a novel remedy for poly cystic ovarian syndrome[106] | Salehpour et al. (2009) | Prospective, double-blind, clinical trial | 6 weeks | NAC: 1800 mg/day, divided into three daily doses; Placebo: ORS, divided into three daily doses | 46 | 5 (27.8%)<br>5 (27.8%) | After the completion of the treatment course, no significant change was observed in the ultrasound results, improvement of acne, hirsutism, and alopecia. |
| Metformin and N-acetyl cysteine in polycystic ovarian syndrome––a comparative study | Gayatri et al. (2010) | A prospective, randomized, controlled study | 3 months | NAC: 1800 mg/day, divided into three oral doses; Metformin: 500 mg/day in week 1; 500 mg twice daily in week 2 and 500 mg thrice daily afterwards | 115 | 1 (2); 2 (4) | After 12 weeks of treatment with NAC, the patients showed a significant decrease in weight gain, hirsutism and acne. |
| Clinical, endocrine and metabolic effects of metformin vs N-acetyl-cysteine in women with polycystic ovary syndrome[102] | Oner and Muderris (2011) | Prospective trial | 24 weeks | NAC: 1800 mg/day, divided into three oral doses; Metformin: 1500 mg/day, divided into three oral doses | 100 | NA | Following the treatment, LH, total testosterone and free testosterone decreased significantly, and SHBG increased significantly in both groups. The clinical manifestations of hirsutism also improved significantly in both groups compared to baseline. |
| N-acetylcysteine as an adjuvant to clomiphene citrate for successful induction of ovulation in infertile patients with polycystic ovary syndrome[108] | Salehpour et al. (2012) | Placebo-controlled, double-blind, randomized, clinical trial | From day 3 until day 7 of the menstrual cycle | NAC: 1200 mg/day, divided into two daily doses; Placebo: ORS, divided into two daily doses | 180 | NA | Based on our data, a significantly better ovulation rate was observed in the PCOS patients who received NAC as an adjuvant to CC for the induction of ovulation. Since insulin resistance has been shown to be a cause of CC failure in both obese and nonobese PCOS patients, the potential insulin-sensitizing effects of NAC may have led to the better induction of ovulation in these patients. |

**TABLE 3** (Continued)

| NAC and PCOS | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Study ID** | **Design** | **Duration of treatment** | **Treatment arms** | **Number of patients** | **Number of patients with acne (%)** | **Conclusion(s)** |
| N-acetyl-cysteine is a novel adjuvant to clomiphene citrate in clomiphene citrate–resistant patients with polycystic ovary syndrome[109] | Rizk et al. (2005) | Placebo-controlled, double-blind, randomized trial | 5 days, starting on day 3 of the cycle | NAC(group I):1.2 g/dPlacebo (group II): CC 100 mg/d | 153 | NA | NAC can be used as an alternative to other insulin-sensitizing agents like metformin or troglitazone. The effects of NAC therapy on the hormonal and metabolic profiles, symptoms of hyperandrogenism, and cardiovascular risk factors need further assessment. |
| N-acetyl cysteine vs. metformin in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective randomized controlled study[110] | Elnashar et al. (2007) | Prospective, randomized, controlled study | 6 weeks | NAC: 1800 mg/day, divided into three oral doses; Metformin: 1500 mg/day, divided into three oral doses | 64 | NA | In the NAC group, there were no significant differences in fasting glucose or fasting insulin, and there was a significant decrease in total T before and after the treatment. |
| N-acetyl cysteine plus clomiphene citrate versus metformin and clomiphene citrate in treatment of clomiphene-resistant polycystic ovary syndrome[111] | Hashim et al. (2010) | Randomized Controlled Trial | 3 treatment cycles | NAC: 1800 mg/day, divided into three oral doses; Metformin: 1500 mg/day, divided into three oral doses | 192 | NA | The efficacy of metformin-CC combination therapy is higher than that of NAC-CC for inducing ovulation and achieving pregnancy among CC-resistant PCOS patients. |
| Effect of N-acetyl-cysteine after ovarian drilling in clomiphene citrate-resistant PCOS women[112] | Nasr (2010) | Pilot study | 5 days, starting on day 3 of the cycle for 12 consecutive cycles | NAC: 1200 mg/day, divided into two daily doses; Placebo: ORS, divided into two daily doses | 60 | NA | NAC may help improve the reproductive outcome in women undergoing unilateral LOD for clomiphene citrate-resistant PCOS. |

(Continues)

**TABLE 3** (Continued)

| NAC and PCOS | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Study ID** | **Design** | **Duration of treatment** | **Treatment arms** | **Number of patients** | **Number of patients with acne (%)** | **Conclusion(s)** |
| Efficacy of combination therapy of inositols, antioxidants and vitamins in obese and nonobese women with polycystic ovary syndrome: an observational study[113] | Kamal Advani (2019) | Retro prospective, observational, multi-centric study | 12 weeks | One tablet of Trazer F ForteTM (CORONA Remedies Pvt. Ltd.) twice daily. (combination of inositols (MI:DCI) 600 mg þ NAC 300 mg þ Biotin 5 mg þ 10% Lycopene 5 mg þ Chromium picolinate 200 mcg þ Folic Acid 120 mcg þ Vitamin D 400 IU) | 67 | 44 | A significant improvement was observed in menstrual cyclicity, acne and hirsutism in both obese and underweight PCOS patients. |
| Randomized controlled trial of N-acetylcysteine vs l-carnitine among women with clomiphene-citrate-resistant polycystic ovary syndrome[114] | El Sharkwy (2019) | Double-blind, randomized, controlled, clinical trial | 3 months | N-acetylcysteine group: 150 mg/day of CC from day 3 until day 7 of the menstrual cycle (Clomid, Global Napi, Cairo, Egypt) plus 600 mg of oral N-acetylcysteine (a sachet of powder for dilution in water; Sedico Co., Cairo, Egypt) three times daily, and a placebo capsule similar to the l-carnitine capsule. l-carnitine group: 150 mg/day of CC from day 3 until day 7 of the menstrual cycle plus3g of oral l-carnitine (N A l-Carnitine; Mepaco, Cairo, Egypt) daily, and placebo sachets containing an oral rehydration solution specifically designed to look similar to those containing N-acetylcysteine | 162 | NA | There was a significant improvement in the menstrual pattern, FSH, LH, free testosterone, and insulin resistance markers (FG, FI, FG/FI ratio, HOMA index) in both groups ($P < .001$ for all). There was no significant difference in terms of changes in BMI, menstrual pattern, FSH, or LH between the two groups. However, the N-acetylcysteine group showed greater improvement in free testosterone, FG, FI, FG/FI ratio, and HOMA index ($P < .05$ for all) compared to the l-carnitine group. |
| N-acetylcysteine as an adjuvant to letrozole for | Mostajeran (2018) | Placebo-controlled, double-blind, randomized, clinical trial | 5 days, starting on day 3 of menstruation | Group 1: letrozole 5 mg/day plus NAC 1.2 g/day | 130 | NA | NAC was demonstrated to be a safe and well-tolerated adjuvant to |

**TABLE 3** (Continued)

| NAC and PCOS | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Study ID** | **Design** | **Duration of treatment** | **Treatment arms** | **Number of patients** | **Number of patients with acne (%)** | **Conclusion(s)** |
| induction of ovulation in infertile patients with polycystic ovary syndrome[115] | | | | Group 2: letrozole plus placebo | | | letrozole that can increase pregnancy rates in PCOS patients. |
| Comparison of metformin and N-acetyl cysteine, as an adjuvant to clomiphene citrate, in clomiphene-resistant women with polycystic ovary syndrome[116] | Nemati (2017) | Clinical trial | 8 and 12 weeks | One group (54 PCOS patients with CC resistance) received NAC at a dose of 1800 mg/day in three daily doses (each dose was 600 mg and was administered three times a day to the patients) on the third day of the menstrual cycle. The other group (54 CC-resistant PCOS patients) took 500-mg metformin three times a day on day 3 of the menstrual cycle (total concentration of metformin given to the patients was 1500 mg/day) | 108 | NA | NAC administration did not have any effects on the hirsutism score and hormonal profile after 8 weeks; however, long-term treatment with NAC significantly reduced the hirsutism score and serumconcentrations of SHBG, testosterone, fasting insulin, and FBS. |
| A comparison between the effects of metformin and N-acetyl cysteine (NAC) on some metabolic and endocrine characteristics of women with polycystic ovary syndrome[117] | Forough Javanmanesh (2015) | Randomized, double-blind, clinical trial | 24 weeks | One group: oral NAC 600 mg, three times a day; Other group: 500 mg oral metformin, three times a day | 120 | NA | In this study, both metformin and NAC improved the lipid profile, BMI, AUB and fasting blood sugar and insulin, whereas therewere no differences between the two groups before the treatment. After the treatment, NAC improved BMI, AUB, FBS and fasting insulin and lipid profile more than metformin. |

(Continues)

**TABLE 3** (Continued)

| NAC and PCOS | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **Study ID** | **Design** | **Duration of treatment** | **Treatment arms** | **Number of patients** | **Number of patients with acne (%)** | **Conclusion(s)** |
| The adjuvant effect of metformin and N-acetylcysteine to clomiphene citrate in induction of ovulation in patients with polycystic ovary syndrome[118] | Maged (2015) | Prospective randomized study | Treatment was repeated in nonpregnant cases for three successive cycles | Group I (40 patients) received no further treatment. Group II (40 patients) received 1200 mg NAC (acetylcysteine, SEDICO CO., Egypt) in two divided doses in the form of powder inserted in small pockets to be dilutedinto one standard glass of water from day 3 until day 7 of themenstrual cycle. Group 3 (40 patients) received metformin 500 mg (cidophage 500 mg, CID CO., Egypt) three times daily continuously. All the patients received CC (clomid global Napi, 6th October, Egypt) 100 mg orally in two divided doses from day 3 until day 7 of the menstrual cycle | 120 | NA | NAC as an adjuvant to CC for the induction of ovulation improves ovulation and pregnancy rates in PCOS patients and has beneficial impacts on endometrial thickness. |
| N-Acetylcysteine improves oocyte and embryo quality in polycystic ovary syndrome patients undergoing intracytoplasmic sperm injection: an alternative to metformin[119] | Ebrahim Cheraghi (2014) | Prospective, randomized, placebo-controlled, pilot | 6 weeks | Group1:1500 mg/d MET Group2:1800 mg/d NAC Group3:NAC + MET Group4: Placebo | 60 | | Malondialdehyde levels decreased significantly in the NAC and NAC + MET groups compared to the placebo-treated group ($P < .02$). In addition, there were significant decreases in leptin levels in the NAC, MET and NAC + MET groups compared to the placebo group ($P < .001$). Insulin and LH levels were significantly lower in the MET and NAC groups compared to the placebo-treated group ($P < .02$). |

## 4 | CONCLUSION

N-acetyl-cysteine has multipotential qualities (antioxidant, antibacterial, anti-keratinize, anti-fibrosis, anti-excoriation, etc.) and a limited number of studies have demonstrated its healing properties for acne lesions and acne associated outcomes in both oral and topical forms. Further studies are needed to prove these effects. This systematic review article focuses on all pathomechanisms of acne vulgaris and the potential roles of NAC for controlling and treating these events also proper characteristics of NAC regarding acne related outcomes like excoriations and scars or conditions are associated with acne emergence and its severity or resistance like PCODs.

### ACKNOWLEDGEMENT

The authors would like to thank Rasool Akram Medical Complex Clinical Research Development Center (RCRDC) for its technical and editorial assist.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTIONS

All authors contributed for preparing and finalization of this article. Nafiseh Mardani and Samaneh Mozafarpoor substantial contributions to conception and design, Samaneh Mozafarpoor and Azadeh Goodarzi were involved in drafting the manuscript; Nafiseh Mardani, Samaneh Mozafarpoor, and Farahnaz Nikkhah revised the paper critically for important intellectual content. Azadeh Goodarzi: revised, searched the literature and submitted first and final version. Samaneh Mozafarpoor and Azadeh Goodarzi was involved in acquision of data and analysis of first and revised version of the article; Samaneh Mozafarpoor and Farahnaz Nikkhah (new author) contributed equally in editing, searching the literature and revising the final version. All authors contributed in gave final approval of the version to be published. The team has participated sufficiently in the work to take public responsibility for appropriate portions of the content, and was greed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### DATA AVAILABILITY STATEMENT

The authors agree with sharing, coping, and modifying the data used in this article, even for commercial purposes. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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### REFERENCES

1. Picardo M, Eichenfield LF, Tan J. Acne and Rosacea. *Dermatol Ther(Heidelb)*. 2017;7(S1):43-52.
2. Zouboulis CC, Jourdan E, Picardo M. Acne is an inflammatory disease and alterations of sebum composition initiate acne lesions. *J Eur Acad Dermatol Venereol*. 2014;28(5):527-532.
3. Hay RJ, Johns NE, Williams HC, et al. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol*. 2014;134(6):1527-1534.
4. Tan JK, Bhate K. A global perspective on the epidemiology of acne. *Br J Dermatol*. 2015;172(Suppl 1):3-12.
5. Cresce ND, Davis SA, Huang WW, Feldman SR. The quality of life impact of acne and rosacea compared to other major medical conditions. *J Drugs Dermatol*. 2014;13(6):692-697.
6. Tan X, Al-Dabagh A, Davis SA, et al. Medication adherence, healthcare costs and utilization associated with acne drugs in Medicaid enrollees with acne vulgaris. *Am J Clin Dermatol*. 2013;14(3):243-251.
7. Karimkhani C, Dellavalle RP, Coffeng LE, et al. Global skin disease morbidity and mortality: an update from the global burden of disease study 2013. *JAMA Dermatol*. 2017;153(5):406-412.
8. Awan S, Lu J. Management of severe acne during pregnancy: a case report and review of the literature. *Int J Women Dermatol*. 2017;3(3):145-150.
9. Layton A, Eady EA, Peat M, et al. Identifying acne treatment uncertainties via a James Lind Alliance priority setting partnership. *BMJ Open*. 2015;5(7):e008085.
10. Ochsendorf FR, Degitz K. Medikamentöse Therapie der Akne. *Hautarzt*. 2008;59(7):579-590.
11. Brok J, Buckley N, Gluud C. Interventinss for paracetamol (acetaminophen) overdose. *Cochrane Database Syst Rev*. 2006;2:CD003328.
12. N-acetyl-L-cysteine. National Center for Biotechnology Information. Pubchem Compound Database; CID 12035.
13. Pei Y, Liu H, Yang Y, et al. Biological activities and potential oral applications of N-acetylcysteine: Progress and prospects. *Oxid Med Cell Longev*. 2018;2018:2835787.
14. Bavarsad Shahripour R, Harrigan MR, Alexandrov AV. N-acetylcysteine (NAC) in neurological disorders: mechanisms of action and therapeutic opportunities. *Brain Behav*. 2014;4:108-122.
15. Atkuri KR, Mantovani JJ, Herzenberg LA, Herzenberg LA. N-acetylcysteine: a safe antidote for cysteine/glutathione deficiency. *Curr Opin Pharmacol*. 2007;7:355-359.
16. Millea PJ. N-acetylcysteine: multiple clinical applications. *Am Fam Physician*. 2009;80:265-269.
17. Dodd S, Dean O, Copolov DL, Malhi GS, Berk M. N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility. *Expert Opin Biol Ther*. 2008;8:1955-1962.
18. Gurbuz AK, Ozel AM, Ozturk R, Yildirim S, Yazgan Y, Demirturk L. Effect of N-acetyl cysteine on *Helicobacter pylori*. *South Med J*. 2005;98(11):1095-1109.
19. Adi M, Amin SS, Mohtashim M, et al. N-acetylcysteine in dermatology. *Indian J Dermatol Venereol Leprol*. 2018;84(6):652-659.
20. Janeczek M, Moy L, Riopelle A, et al. The potential uses of N-acetylcysteine in dermatology: a review. *J Clin Aesthet Dermatol*. 2019;12(5):20-26.
21. Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol*. 2013;168(3):474-485.
22. Webster GF. The pathophysiology of acne. *Cutis*. 2005;76(Suppl 2):4-7.
23. Thiboutot DM, Dréno B, Abanmi A, et al. Practical management of acne for clinicians: an international consensus from the global alliance to improve outcomes in acne. *J Am Acad Dermatol*. 2018;78(2S1):S1-S23.
24. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a global alliance to improve outcomes in acne. *J Am Acad Dermatol*. 2003;49(Suppl 1):S1-S37.
25. Gebauer K. Acne in adolescents. *Aust Fam Physician*. 2017;46(12):892-895.

26. Gollnick HP, Bettoli V, Lambert J, et al. A consensus-based practical and daily guide for the treatment of acne patients. *J Eur Acad Dermatol Venereol*. 2016;30(9):1480-1490.
27. Smithard A, Glazebrook C, Williams HC. Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence:a community based study. *Br J Dermatol*. 2001;145(2):274-279.
28. Eyuboglu M, Kalay I, Eyoboglu D. Evaluation of adolescents diagnosed with acne vulgaris for quality of life and psychosocial challenges. *Indian J Dermatol*. 2018;63(2):131-135.
29. Gallitano SM, Berson DS. How acne bumps cause the blues: the influence of acne vulgaris on self-esteem. *Int J Womens Dermatol*. 2017;4(1):12-17.
30. Eroglu FO, Aktepe E, Erturan I. The evaluation of psychiatric comorbidity, self-injurious behavior, suicide probability, and other associated psychiatric factors (lonileness, self-esteem, life satisfaction) in adolescents with acne: a clinical pilot study. *J Cosmet Dermatol*. 2018;18(3):916-921.
31. Dunn LK, O'Neill JL, Feldman SR. Acne in adolescents: quality of life, self-esteem, mood, and psychological disorders. *Dermatol Online J*. 2011;17(1):1.
32. Tan J, Kang S, Leyden J. Prevalence and risk factors of acne scarring among patients consulting dermatologists in the USA. *J Drugs Dermatol*. 2017;16(2):97-102.
33. Mwanthi M, Zaeglein L. Update in the management of acne in adolescents. *Curr Opin Pediatr*. 2018;30(4):492-498.
34. Eichenfield LF, Krakowski AC, Piggott C, et al. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. *Pediatrics*. 2013;131(Suppl 3):S163-S186.
35. Webster GF. Inflammation in acne vulgaris. *J Am Acad Dermatol*. 1995;33(2):247-253.
36. Hunt DW, Winters GC, Brownsey RW, et al. Inhibition of sebum production with the acetyl coenzyme a carboxylase inhibitor olumacostat glasaretil. *J Invest Dermatol*. 2017;137(7):1415-1423.
37. Ottaviani M, Alestas T, Flori E, Mastrofrancesco A, Zouboulis CC, Picardo M. Peroxidated squalene induces the production of inflammatory mediators in HaCaT keratinocytes:a possible role in acne vulgaris. *J Invest Dermatol*. 2006;126(11):2430-2437.
38. Cunliffe WJ, Holland DB, Clark SM, Stables GI. Comedogenesis: some new aetiological, clinical and therapeutic strategies. *Br J Dermatol*. 2000;142(6):1084-1109.
39. Cunliffe WJ, Simpson NB. Disorders of the sebaceous gland. In: Champion RH, Burton JL, Burns DA, et al., eds. *Textbook of Dermatology*. 6th ed. Oxford: Blackwell Science; 1998:1927-1984.
40. Haider A, Shaw JC. Treatment of acne vulgaris. *JAMA*. 2004;292(6):726-735.
41. Layton AM. A review on the treatment of acne vulgaris. *Int J Clin Pract*. 2006;60(1):64-72.
42. Fox L, Csongradi C, Aucamp M, du Plessis J, Gerber M. Treatment modalities for acne. *Molecules*. 2016;21(8):1063.
43. Leyden JJ. Therapy for acne vulgaris. *New Engl J Med*. 1997;336(16):1156-1162.
44. Narahari S, Gustafson C, Feldman S. What's new in antibiotics in the management of acne? *G Ital Dermatol Venereol*. 2012;147(3):227-238.
45. Valente Duarte De Sousa IC. New and emerging drugs for the treatment of acne vulgaris in adolescents. *Expert Opin Pharmacother*. 2019;20(8):1009-1024.
46. Sarici G, Cinar S, Armutcu F, Altinyazar C, Koca R, Tekin NS. Oxidative stress in acne vulgaris. *J Eur Acad Dermatol Venereol*. 2010;24:763-767.
47. Chiba K, Yoshizawa K, Makino I, Kawakami K, Onoue M. Changes in the levels of glutathione after cellular and cutaneous damage induced by squalene monohydroperoxide. *J Biochem Mol Toxicol*. 2001;15:150-158.
48. Puhvel SM, Sakamoto M. The chemoattractant properties of comedonal contents. *J Invest Dermatol*. 1978;71:324-329.
49. Webster GF, Leyden JJ, Tsai CC, Baehni P, McArthur WP. Polymorphonuclear leukocyte lysosomal release in response to *Propionibacterium acnes* in vitro and its enhancement by sera from patients with inflammatory acne. *J Invest Dermatol*. 1980;74:398-401.
50. Webster GF, Kligman AM. A method for the assay of inflammatory mediators in follicular casts. *J Invest Dermatol*. 1979;73:266-268.
51. McCord JM, Fridovich I. The biology and pathology of oxygen radicals. *Ann Intern Med*. 1978;89:122-127.
52. Fuchs J, Packer L. Antioxidant protection from solar-simulated radiation-induced suppression of contact hypersensitivity to the recall antigen nickel sulfate in human skin. *Free Radic Biol Med*. 1999;27:422-427.
53. Kurutas EB, Arican O, Sasmaz S. Superoxide dismutase and myeloperoxidase activities in polymorphonuclear leukocytes in acne vulgaris. *Acta Dermatovenerol Alp Panonica Adriat*. 2005;14:39-42.
54. Miyachi Y, Yoshioka A, Imamura S, Niwa Y. Polymorphonuclear leukocyte-derived reactive oxygen species in inflammatory skin diseases. In: Hayaishi O, Imamura S, Miyachi Y, eds. *The Biological Role of Reactive Oxygen Species in Skin*. Tokyo: University of Tokyo Press; 1987:135-140.
55. Akamatsu H, Horio T. The possible role of reactive oxygen species generated by neutrophils in mediating acne inflammation. *Dermatology*. 1998;196:82-85.
56. Akamatsu H, Horio T, Hattori K. Increased hydrogen peroxide generation by neutrophils from patients with acne inflammation. *Int J Dermatol*. 2003;42(5):366-369.
57. Kerksick C, Willoughby D. The antioxidant role of glutathione and N-acetyl-cysteine supplements and exercise-induced oxidative stress. *J Int Soc Sports Nutr*. 2005;2:38-44.
58. Dean O, Giorlando F, Berk M. N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. *J Psychiatry Neurosci*. 2011;36:78-86.
59. Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved inacne lesion initiation. *J Invest Dermatol*. 2003;121:20-27.
60. Holland DB, Jeremey AH. The role of inflammation in the pathogenesis of acne and acne scarring. *Semin Cutan Med Surg*. 2005;24:79-83.
61. Sugisaki H, Yamanaka K, Kakeda M, et al. Increased interferon-gamma, interleukin-12p40 and IL-8 production in *Propionibacterium acnes*-treated peripheral blood mononuclear cells from patient with acne vulgaris: host response but not bacterial species is the determinant factor of the disease. *J Dermatol Sci*. 2009;55(1):47-52.
62. Nascimento MM, Suliman ME, Silva M, et al. Effect of oral N-acetylcysteine treatment on plasma inflammatory and oxidative stress markers in peritoneal dialysis patients: a placebo-controlled study. *Perit Dial Int*. 2010;30:336-342.
63. Chen G, Shi J, Hu Z, Hang C. Inhibitory effect on cerebral inflammatory response following traumatic brain injury in rats: a potential neuroprotective mechanism of N-acetylcysteine. *Mediators Inflamm*. 2008;2008:716458.
64. Gloire G, Piette J. Redox regulation of nuclear post-translational modifications during NF-kappaB activation. *Antioxid Redox Signal*. 2009;11:2209-2222.
65. Sekharam M, Trotti A, Cunnick JM, Wu J. Suppression of fibroblast cell cycle progression in G1 phase by N-acetylcysteine. *Toxicol Appl Pharmacol*. 1998;149:210-216.
66. Redondo P, Bauzá A. Topical N-acetylcysteine for lamellar ichthyosis. *Lancet*. 1999;354:1880.
67. Bassotti A, Moreno S, Criado E. Successful treatment with topical N-acetylcysteine in urea in five children with congenital lamellar ichthyosis. *Pediatr Dermatol*. 2011;28:451-455.

68. Deffenbacher B. Successful experimental treatment of congenital ichthyosis in an infant. *BMJ Case Rep*. 2013;2013:pii:bcr2013008688.
69. Burkhart CG, Burkhart CN, Lehmann PF. Acne: a review of immunologic and microbiologic factors. *Postgrad Med J*. 1999;75:328-331.
70. Gollnick H. Current concepts of the pathogenesis of acne, implications for drug treatment. *Drugs*. 2003;63:1579-1596.
71. McInturff JE, Kim J. The role of toll-like receptors in the pathophysiology of acne. *Semin Cutan Med Surg*. 2005;24:73-78.
72. Tan AW, Tan HH. Acne vulgaris: a review of antibiotic therapy. *Expert Opin Pharmacother*. 2005;6(3):409-418.
73. Eady EA, Gloor M, Leyden JJ. *Propionibacterium acnes* resistance: a worldwide problem. *Dermatology*. 2003;206(1):54-56.
74. Pecastaings S, Roques C, Nocera T, et al. Characterisation of Cutibacterium acnes phylotypes in acne and in vivo exploratory evaluation of Myrtacine. *J Eur Acad Dermatol Venereol*. 2018;32 (Suppl. 2):15-23.
75. Ramage G, Tunney MM, Patrick S, Gorman SP, Nixon JR. Formation of *Propionibacterium acnes* biofilms on orthopaedic biomaterials and their susceptibility to antimicrobials. *Biomaterials*. 2003;24(9):3221-3227.
76. Burkhart CN, Burkhart CG. Microbiology's principle of biofilms as a major factor in the pathogenesis of acne vulgaris. *Int J Dermatol*. 2003;42(12):925-927.
77. Coenye T, Peeters E, Nelis HJ. Biofilm formation by *Propionibacterium acnes* is associated with increased resistance to antimicrobial agents and increased production of putative virulence factors. *Res Microbiol*. 2007;158(4):386-392.
78. Burkhart CG, Burkhart CN. Expanding the microcomedone theory and acne therapeutics: *Propionibacterium acnes* biofilm produces biological glue that holds corneocytes together to form plug. *J Am Acad Dermatol*. 2007;57(4):722-724.
79. Rosen T. The Propionibacterium acne genome: from the laboratory to the clinic. *J Drugs Dermatol*. 2007;6(6):582-586.
80. Bruggemann H, Henne A, Hoster F, et al. The complete genome sequence of *Propionibacterium acnes*, commensal of the skin. *Science*. 2004;305(5684):671-673.
81. Blasi F, Page C, Rossolini GM, et al. The effect of N -acetylcysteine on biofilms: implications for the treatment of respiratory tract infections. *Respir Med*. 2016;117:190-197.
82. Choi YS, Kim C, Moon JH, Lee JY. Removal and killing of multispecies endodontic biofilms by N -acetylcysteine. *Braz J Microbiol*. 2018;49(1):184-188.
83. Quah SY, Wu S, Lui JN, Sum CP, Tan KS. N-Acetylcysteine inhibits growth and eradicates biofilm of *Enterococcus faecalis*. *J Endod*. 2012;38(1):81-85.
84. Moran MM, McFarland K, Melendez RI, Kalivas PW, Seamans JK. Cystine/glutamate exchange regulates metabotropic glutamate receptor presynaptic inhibition of excitatory transmission and vulnerability to cocaine seeking. *J Neurosci*. 2005;25:6389-6393.
85. Gere-Pászti E, Jakus J. The effect of N-acetylcysteine on amphetamine-mediated dopamine release in rat brain striatal slices by ion-pair reversed-phase high performance liquid chromatography. *Biomed Chromatogr*. 2009;23:658-664.
86. Arnold LM, Auchenbach MB, McElroy SL. Psychogenic excoriation: clinical features, proposed diagnostic criteria, epidemiology, and approaches to treatment. *CNS Drugs*. 2001;15(5):351-359.
87. Jafferany M, Patel A. Skin-picking disorder: a guide to diagnosis and management. *CNS Drugs*. 2019;33(4):337-346.
88. Grant JE, Chamberlain SR, Redden SA, Leppink EW, Odlaug BL, Kim SW. N-Acetylcysteine in the treatment of excoriation disorder. *JAMA Psychiat*. 2016;73(5):490-496.
89. Miller JL, Angulo M. An open-label pilot study ofN-acetylcysteine for skin-picking in Prader-Willi syndrome. *Am J Med Genet A*. 2013; 164(2):421-424.
90. Sahib AS, Al-Anbari HH, Salih M, Abdullah F. Effect of oral antioxidants on lesion counts associated with oxidative stress and inflammation in patients with papulopustular acne. *J Clin Exp Dermatol Res*. 2012;3:5.
91. Montes LF, Wilborn WH, Montes CM. Topical acne treatment with acetylcysteine: clinical and experimental effects. *Skinmed*. 2012;10: 348-351.
92. Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nat Rev Endocrinol*. 2018;14(5): 270-284.
93. Dramusic V, Rajan U, Chan P, et al. Adolescent polycystic ovary syndrome. *Ann N Y Acad Sci*. 1997;816:194-208.
94. Azziz R, Marin C, Hoq L, Badamgarav E, Song P. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. *J Clin Endocrinol Metab*. 2005;90(8):4650-4658.
95. Chang WY, Knochenhauer ES, Bartolucci AA, Azziz R. Phenotypic spectrum of polycystic ovary syndrome: clinical and biochemical characterization of the three major clinical subgroups. *Fertil Steril*. 2005;83(6):1717-1723.
96. Jones GL, Benes K, Clark TL, et al. The polycystic ovary syndrome health-related quality of life questionnaire (PCOSQ): a validation. *Hum Reprod*. 2004;19(2):371.
97. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab*. 2004;89(6):2745-2749.
98. Trifu V, Tiplica GS, Naumescu E, Zalupca L, Moro L, Celasco G. Cortexolone 17alpha-propionate 1% cream, a new potent antiandrogen for topical treatment of acne vulgaris. A pilot randomized,double-blind comparative study vs. placebo and tretinoin 0.05% cream. *Br J Dermatol*. 2011;165(1):177-183.
99. Lai JJ, Chan P, Lai KP. The role of androgen and androgen receptor in skin-related disorders. *Arch Dermatol Res*. 2012;304(7):499-510.
100. Fritsch M, Orfanos CE, Zouboulis CC. Sebocytes are the key regulators of androgen homeostasis in human skin. *J Invest Dermatol*. 2001;116(5):793-800.
101. Kelce W. Topical nitric oxide: a first-in-class local antiandrogen therapy for the treatment of acne and male pattern baldness. (white paper). *Novan Therapeut*. 2018;http://www.novan.com/files/8613/7398/9326/Topical_nitric_oxide_local_androgen_therapy.pdf.
102. Oner G, Muderris II. Clinical, endocrine and metabolic effects of metformin vs N-acetyl-cysteine in women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol*. 2011;159(1):127-131.
103. Thakker D, Raval A, Patel I, Walia R. N-acetylcysteine for polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. *Obstet Gynecol Int*. 2015;2015:817849.
104. Percinel I, Yazici KU. Glutamatergic dysfunction in skin-picking disorder. *J Clin Psychopharmacol*. 2014;34(6):772-774.
105. Al-Anbari HH, Sahib AS, Ahmed R, Raghif A. Effects of silymarin, N-acetylcysteine and selenium in the treatment of papulopustular acne. Department of Pharmacology, Al-Nahrain College of Medicine; Department of Pharmacology, Al-Kindy College of Medicine, University of Baghdad; Baghdad, Iraq(2012)
106. Salehpour S, Tohidi M, Akhound MR, Amirzargar N. N acetyl cysteine, a novel remedy for poly cystic ovarian syndrome. *Int J Fertil Steril*. 2009;3(2):66-73.
107. Gayatri K, Kumar JS, Kumar BB. Metformin and N-acetyl cysteine in polycystic ovarian syndrome: a comparative study. *Indian J Clin Med*. 2010;1(1):7-13.
108. Salehpour S, Sene AA, Saharkhiz N, Sohrabi MR, Moghimian F. N-acetylcysteine as an adjuvant to clomiphene citrate for successful induction of ovulation in infertile patients with polycystic ovary syndrome. *J Obstet Gynaecol Res*. 2012;38(9):1182-1186.

109. Rizk AY, Bedaiwy MA, Al-Inany HG. N-acetyl-cysteine is a novel adjuvant to clomiphene citrate in clomiphene citrate-resistant patients with polycystic ovary syndrome. *Fertil Steril*. 2005;83(2):367-370.
110. Elnashar A, Fahmy M, Mansour A, Ibrahim K. N-acetyl cysteine vs. metformin in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective randomized controlled study. *Fertil Steril*. 2007;88(2):406-409.
111. Hashim HA, Anwar K, El-Fatah RA. N-acetyl cysteine plus clomiphene citrate versus metformin and clomiphene citrate in treatment of clomiphene-resistant polycystic ovary syndrome: a randomized controlled trial. *J Women Health*. 2010;19(11):2043-2048.
112. Nasr A. Effect of N-acetyl-cysteine after ovarian drilling in clomiphene citrate-resistant PCOS women: a pilot study. *Reprod Biomed Online*. 2010;20(3):403-409.
113. Advani K, Batra M, Tajpuriya S, et al. Efficacy of combination therapy of inositols, antioxidants and vitamins in obese and non-obese women with polycystic ovary syndrome: an observational study. *J Obstet Gynaecol*. 2019;40(1):1-6.
114. el Sharkwy IA, Abd El Aziz WM. Randomized controlled trial of N -acetylcysteine versus l -carnitine among women with clomiphene-citrate-resistant polycystic ovary syndrome. *Int J Gynecol Obstet*. 2019;147(1):59-64.
115. Mostajeran F, Ghasemi Tehrani H, Rahbary B. N-Acetylcysteine as an adjuvant to letrozole for induction of ovulation in infertile patients with polycystic ovary syndrome. *Adv Biomed Res*. 2018;7:100.
116. Nemati M, Nemati S, Taheri AM, Heidari B. Comparison of metformin and N-acetyl cysteine, as an adjuvant to clomiphene citrate, in clomiphene-resistant women with polycystic ovary syndrome. *J Gynecol Obstet Human Reprod*. 2017;46(7):579-585.
117. Javanmanesh F, Kashanian M, Rahimi M, Sheikhansari N. A comparison between the effects of metformin andN-acetyl cysteine (NAC) on some metabolic and endocrine characteristics of women with polycystic ovary syndrome. *Gynecol Endocrinol*. 2015;32(4):285-289.
118. Maged AM, Elsawah H, Abdelhafez A, Bakry A, Mostafa WA. The adjuvant effect of metformin andN-acetylcysteine to clomiphene citrate in induction of ovulation in patients with Polycystic ovary syndrome. *Gynecoll Endocrinol*. 2015;31(8):635-638.
119. Cheraghi E, Mehranjani MS, Shariatzadeh MA, Esfahani MHN, Ebrahimi Z. N-Acetylcysteine improves oocyte and embryo quality in polycystic ovary syndrome patients undergoing intracytoplasmic sperm injection: an alternative to metformin. *Reprod Fertil Dev*. 2016;28(6):723.
120. Goodman GJ. Post-acne scarring: a review of its pathophysiology and treatment. *Dermatol Surg*. 2000;26(9):857-871.
121. Chuah SY, Goh CL. The impact of post-acne scars on the quality of life among young adults in Singapore. *J Cutun Aesthet Surg*. 2015;8 (3):153-158.
122. Goodman GJ. Treatment of acne scarring. *Int J Dermatol*. 2011;50 (10):1179-1194.
123. Lee WJ, Jung HJ, Lim HJ, Jang YH, Lee SJ, Kim DW. Serial sections of atrophic acne scars help in the interpretation of microscopic findings and the selection of good therapeutic modalities. *J Eur Acad Dermatol Venereol*. 2013;27:643-646.
124. Holland DB, Jeremy AH, Roberts SG, et al. Inflammation in acne scarring: a comparison of the responses in lesions from patients prone and not prone to scar. *Br J Dermatol*. 2004;150:72-81.
125. Saint-Jean M, Khammari A, Jasson F, Nguyen JM, Dréno B. Different cutaneous innate immunity profiles in acne patients with and without atrophic scars. *Eur J Dermatol*. 2016;26:68-74.
126. Connolly D, Vu HL, Mariwalla K, Saedi N. Acne scarring: pathogenesis, evaluation, and treatment options. *J Clin Aesthet Dermatol*. 2017; 10(9):12-23.
127. Pereira-Filho G, Ferreira C, Schwengber A, Marroni C, Zettler C, Marroni N. Role of N-acetylcysteine on fibrosis and oxidative stress in cirrhotic rats. *Arq Gastroenterol*. 2008;45:156-162.
128. Galicia-Moreno M, Rodríguez-Rivera A, Reyes-Gordillo K, et al. N-acetylcysteine prevents carbon tetrachloride-induced liver cirrhosis: role of liver transforming growth factor-beta and oxidative stress. *Eur J Gastroenterol Hepatol*. 2009;21:908-914.
129. Demiroren K, Dogan Y, Kocamaz H. Protective effects of L-carnitine, N-acetylcysteine and genistein in an experimental model of liver fibrosis. *Clin Res Hepatol Gastroenterol*. 2014;38(1):63-72.
130. Ozkaya H, Bahat G, Tufan A, Dogan H, Bilicen Z, Karan MA. Successful treatment of non-healing pressure ulcers with topical n-acetyl cysteine. *J Wound Care*. 2015;24(606):608-611.
131. Deniz M, Borman H, Seyhan T, Haberal M. An effective antioxidant drug on prevention of the necrosis of zone of stasis: N-acetylcysteine. *Burns*. 2013;39:320-325.
132. Demir EO, Cakmak GK, Bakkal H, et al. N-acetyl-cysteine improves anastomotic wound healing after radiotherapy in rats. *J Invest Surg*. 2011;24:151-158.
133. Aktunc E, Ozacmak VH, Ozacmak HS, et al. N-acetyl cysteine promotes angiogenesis and clearance of free oxygen radicals, thus improving wound healing in an alloxan-induced diabetic mouse model of incisional wound. *Clin Exp Dermatol*. 2010;35: 902-909.
134. Rosato E, Veneziano ML, di Mario A, Molinaro I, Pisarri S, Salsano F. Ulcers caused by bullous morphea: successful therapy with N-acetylcysteine and topical wound care. *Int J Immunopathol Pharmacol*. 2013;26:259-262.
135. Lajevardi V, Ghodsi SZ, Daneshpazhooh M, et al. The relationship between body mass index and the severity of acne. *Iran J Dermatol*. 2014;17:13-17.
136. Goodarzi A, Rohaninasab M, Atefi M, et al. Determination of serum levels of zinc in acne vulgaris: a case control study. *Iran J Dermatol*. 2020;23:28-31.
137. Goodarzi A, Behrangi E, Ghassemi M, et al. Comparative serum levels of calcium, vitamin-D, phosphorous and C-reactive protein between acne patients and healthy subjects. *Iran J Dermatol*. 2020; 23:16-20.
138. Goodarzi A, Rohaninasab M, Behrangi E, et al. Serum parameters, diet and body mass index in acne vulgaris: a mini review. *Iran J Dermatol*. 2020;23:32-34.
139. Elham B, Somayeh S, Afsaneh SB, et al. The effect of metformin in the treatment of intractable and late onset acne: a comparison with oral isotretinoin. *Iran J Dermatol*. 2019;22:47-52.
140. Goodarzi A, Mozafarpoor S, Bodaghabadi M, Mohamadi M. The potential of probiotics for treating acne vulgaris: A review of literature on acne and microbiota. *Dermatol Ther*. 2020;33:e13279.
141. Mehran G, Sepasgozar S, Rohaninasab M, et al. Comparison between the therapeutic effect of microneedling versus tretinoin in patients with comedonal acne: a randomized clinical trial. *Iran J Dermatol*. 2019;22:87-91.
142. Goodarzi A. Non-medical treatments for inflammatory acne vulgaris: a comprehensive review on laser, radiofrequency and microneedling. *Iran J Dermatol*. 2019;22:97-106.
143. Behrangi E, Goodarzi A, Roohaninasab M, et al. A review of scar treatment related to acne and burn. *J Crit Rev*. 2020;7(4): 714-722.
144. Goodarzi A, Behrangi E, Ghassemi M, et al. Acne scar: a review of classification and treatment. *J Crit Rev*. 2020;7(7):1108-1114.
145. Atefi N, Behrangi E, Mozafarpoor S, Seirafianpour F, Peighambari S, Goodarzi A. N-acetylcysteine and coronavirus disease 2019: may it work as a beneficial preventive and adjuvant therapy? A Comprehensive Review Study. *J Res Med Sci*. 2020;25:109.
146. Najar Nobari N, Seirafianpour F, Mashayekhi F, Goodarzi A. A systematic review on treatment-related mucocutaneous reactions in COVID-19 patients. *Dermatol Ther*. 2020;34(1): e14662.

147. Nobari NN, Goodarzi A. Patients with specific skin disorders who are affected by COVID-19: what do experiences say about management strategies? A systematic review. *Dermatol Ther*. 2020;33(6):e13867.
148. Seirafianpour F, Sodagar S, Pour Mohammad A, et al. Cutaneous manifestations and considerations in COVID-19 pandemic: a systematic review. *Dermatol Ther*. 2020;33(6):e13986.
149. Seirafianpour F, Mozafarpoor S, Fattahi N, Sadeghzadeh-Bazargan A, Hanifiha M, Goodarzi A. Treatment of COVID-19 with pentoxifylline: could it be a potential adjuvant therapy? *Dermatol Ther*. 2020;33(4):e13733.

**How to cite this article:** Mardani N, Mozafarpoor S, Goodarzi A, Nikkhah F. A systematic review of N-acetylcysteine for treatment of acne vulgaris and acne-related associations and consequences: Focus on clinical studies. *Dermatologic Therapy*. 2021;e14915. https://doi.org/10.1111/dth.14915