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[Overview of Reviews Protocol]

Topical, light-based, and complementary interventions for acne: an overview of systematic reviews

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (overview). The objectives are as follows:

To synthesise the existing evidence on the efficacy and safety of non-systemic pharmacological interventions in the treatment of acne vulgaris and related skin complications.

BACKGROUND

Description of the condition

Acne: clinical manifestations, prevalence, aetiology, risk factors, and social burden

Acne is a chronic inflammatory and immune-mediated disease of the pilosebaceous unit. Clinically, it is characterised by non-inflammatory (open and closed comedones) and inflammatory (papules, pustules, nodules, and cysts) lesions. It is diagnosed by physical examination. Lesions may be present on the face, thorax, and back with variable severity. Acne fulminans and acne conglobata are rare and severe forms of the condition (Williams 2012).

According to the Global Burden of Disease study, acne vulgaris is a highly prevalent disease, affecting 231 million people of both sexes in 2019, and causing 4.96 million YLDs (years lived with a disability) (Lancet Global Health Metrics 2019). It exhibits a global distribution with a growing prevalence, mainly within the population between 15 and 19 years of age (Lynn 2016). Acne is one of the three most prevalent cutaneous diseases in different regions of the globe (Bhate 2013; Tan 2015; Wolkenstein 2003). Although some epidemiological studies have demonstrated differences regarding acne prevalence in different ethnicities (Davis 2010; Quarles 2007), there is no definitive evidence that a biological difference in acne pathogenesis can explain higher prevalence or severity of the disease amongst specific ethnic groups. Recent epidemiological studies from high-income countries tend to show an increased prevalence of acne amongst dark-skinned participants, which seems to be associated with the progressive improvement of the access to healthcare services in these regions of the globe during the last two decades (Lynn 2016). The prevalence amongst 452 adolescents aged between 10 and 17 (mean 13.3 years) from elementary and high school in Sao Paulo city, Brazil was 96.0%, increasing with age; acne was present in 100% of those over 14 years, and was predominately facial and of the comedonal type (61.1%) (Bagatin 2014). Acne is thought to affect 95% of adolescent boys and 85% of adolescent girls. For girls, the onset of the disease occurs between 11 to 13 years, worsening around 18 years; for boys, the onset is between 13 to 14 years, worsening around 19 to 21 years (Ghodsi 2009; Wei 2010). Acne may persist after adolescence (after 25 years of age), or occur for the first time in adulthood (late-onset acne). It may also recur in adults many years after puberty. Prevalence of acne amongst the population over 25 years of age has been increasing in the last 30 years; women represent the majority of affected individuals in this age range (Goulden 1999; Khunger 2012).

Acne is a multifactorial disease. Many aetiopathogenic factors are involved, but chronic inflammation is considered the central one. It has been demonstrated histologically that inflammation is present before the development of clinical inflammatory lesions (Rocha 2014). The activity of sebaceous glands starts at puberty through the linkage of androgens, especially dihydrotestosterone, to nuclear receptors of sebocytes, with subsequent increased lipogenesis and qualitative changes in sebum. The androgens also stimulate follicular hyperkeratinisation. In vitro studies have demonstrated the metabolism of sebaceous glands (Schneider 2018). A specific phylotype (IA1) of *Cutibacterium acnes* (previously named *Propioniobacterium acnes*) predominates in the follicles, and its recognition by toll-like receptor 2, present in sebocytes, keratinocytes, and monocytes, activates nuclear pathways, like the nuclear factor kappa B (*NF-κB*), with cytokines production, and the activator protein 1 (*AP1*), with metalloproteinases release (Dréno 2018). Histologic and immunohistochemical studies have shown a variety of inflammatory mediators in acne-prone skin, such as: interleukin (IL)-1, IL-6, tumour necrosis factor alpha (TNF-α), insulin-like growth factor 1 (*IGF-1*) and insulin-like growth factor 1 receptor (*IGF-1R*), peroxisome proliferator-activated receptor-gamma (*PPAR gamma*) and T helper (Th) cells Th 1 and 17 (Agak 2018). Studies of the influence of occidental insulinogenic diet with high glycaemic load have suggested the specific role of *IGF-1* and *IGF-1R* in acne pathogenesis, increasing sebum production. The mechanism is related to a deviation of forkhead box O1 (*FoxO1*)/ mechanistic target of rapamycin complex 1 (*mTORC1*) signalling, with increased activation of *mTORC1* and deficiency of *FoxO1* (Melnik 2016). Neurohormones from hypothalamus (corticotrophin-releasing hormone) and hypophysis (adrenocorticotropic hormone, prolactin, growth hormone, alpha-Melanocyte-stimulating hormone) also regulate the sebocytes, by direct stimulation or by increasing the sensitivity to testosterone derivatives (Clayton 2020). In adult women, the presence of polycystic ovarian syndrome, with or without hormonal alterations, in addition to hirsutism and menstrual irregularities, are important risk factors for acne (Bansal 2020). There has recently been a relevant discussion about the role of skin and gut microbiome in acne. This involves the decreased diversity of cutaneous and intestinal flora caused by prolonged use of oral and topical antibiotics, which affects host-microbiome interactions and cutaneous barrier in individuals with acne, with release of pro-inflammatory cytokines (Deng 2018; O'Neill 2018; Rocha 2018).

Complications of acne: clinical manifestations, incidence rate

As a common complication, scarring is caused by appearance change and histopathological change of normal skin tissue after skin injury. Skin damage during the healing of active acne may cause scars. Active scars may last 10 years or more, whilst acne scars may last for a lifetime (Abdel Hay 2016). Scars can be classified into four categories according to histological morphology and morphological differentiation, as follows.

- Superficial scar: damage involves the epidermis or dermis surface layer. The surface is rough, and may be accompanied by pigment changes, partially flat and soft. The scar may have unclear boundaries with the surrounding normal skin, but there is generally no dysfunction.
- Hypertrophic scar: damage involves the deep dermis. The scar is higher than the surrounding normal skin, and thickened or hardened locally. At the early stage, the surface of the scar is red for capillary congestion, and the main symptoms are itching and pain. At hypertrophic stage, the hyperaemia decreases, the surface colour becomes lighter, and the scar gradually becomes soft and flat, with itchy symptoms having been relieved or disappeared (Chen 2020).
- Atrophic scar: damage involves the whole skin layer and subcutaneous adipose tissue. The scar is hard, flat, or slightly higher than the surface of the skin. It is closely adhered to the deep tissue, and its local blood circulation is poor. Its colour is light red or white. Its weak epidermis cannot withstand external friction and load, therefore it is easy to rupture, thus forming a chronic ulcer (Fabbrocini 2010).

- Keloid: relevant clinical manifestation is a mass that is higher than the surrounding normal skin and grows continuously beyond the site of the original lesion, with hard texture, poor elasticity, and local itching or pain (Fabbrocini 2010; Jacob 2001).

Acne scars are usually hypertrophic, atrophic, or keloid. Patients may have one or more categories of acne scar in the same skin area (Abdel Hay 2016). The incidence rate of acne scar is about 20% to 30% in individuals with acne (Lauermann 2016). Amongst those with acne scars, the scars on the head and face are mostly at the malar region and the top of the forehead, whilst the incidence rate at the nose and the lower jaw is relatively low. The incidence rate of acne scars at the front chest and back regions was 8.2% and 17%, respectively (Lauermann 2016). In those acne, after skin injury, there may be a series of wound-healing events, which involve three stages: inflammation, granulation tissue formation, and matrix remodelling (Rivera 2007). The formation of scar is mainly related to the number and activation state of inflammatory cells at the wound site. The regulation mechanism for tissue repair and regeneration may be lost in the abnormal fibre wound-healing process (Cowin 1998; Wolfram 2009).

The micro-organisms associated with acne infection include *Propionibacterium acnes*, *Staphylococcus epidermidis*, *Proteus*, Firmicutes, *Actinomyces*, *Streptococcus*, and *Malassezia* (Balato 2019). If not treated timely, acne may develop into acute pyogenic lesions, the clinical manifestations of which are systemic symptoms such as fever, chills, enlarged lymph nodes, and leukocytosis. Many individuals with acne have cysts and pustules due to microbial infection, but most receive proper treatment. In rare cases infection leads to acute suppurative lesions; however, their incidence remains unknown due to lack of data.

Acne can seriously affect patients' mental health, especially those with severe acne. Acne tends to occur in adolescents, and can be emotionally devastating at this stage of life when self-image is emphasised (Lauermann 2016). Anxiety, depression, and even suicidal tendency may appear in those with acne (Lukaviciute 2017), with risk influenced by disease severity, local pigmentation, and scar formation. Acne has a huge impact on the quality of life of those affected (Alanazi 2018). Several studies have identified a close two-way relationship between mental stress and acne (Ramrakha 2016; Wen 2015). In a competitive, modern world where good appearance is often considered advantageous, people with acne can suffer feelings of low self-confidence, rejection, and are often humiliated by others (Cenk 2020). Positive treatment helps improve the psychological state of those with acne. It may alleviate feelings of depression and anxiety and improve quality of life (Kaymak 2009). Individuals with acne therefore need not only medication to alleviate their symptoms, but also timely psychological intervention as necessary, so as to avoid the occurrence of mental illness.

Description of the interventions

The goal of acne therapy is to alleviate local symptoms of acne, improve skin appearance, prevent or minimise potential adverse psychological effects, and alleviate scar formation or relevant symptoms (Cao 2015). Treatment methods depend on the type and degree of acne and associated complications (Gollnick 2003b); the main therapies involve inhibiting the secretion of sebaceous glands, controlling the reproduction of *Propionibacterium acnes*, regulating hormone levels in the body, and alleviating relevant inflammation. An appropriate drug for topical use is enough for individuals with mild acne. For those with moderate or severe acne, for which drugs for topical use are not as effective, combinations of drugs for topical use with oral drugs are adopted for the majority of patients (Akhavan 2003). Drugs for topical use include benzoyl peroxide, topical antibiotics (e.g. clindamycin and erythromycin), topical retinoids A (e.g. tretinoin, adapalene, tazarotene), azelaic acid, dapsone, salicylic acid, topical nicotinamide, sulphur, zinc, and alpha-hydroxy acid (Liu 2020a; Yang 2020; Zaenglein 2016). In addition, some non-pharmacological therapies may treat acne effectively, including physical therapies (e.g. radiofrequency therapy and light therapy) (Barbaric 2016), complementary therapies (e.g. herbal medicine, tea tree oil, biological feedback therapy, diet and nutrition, manual therapy, biological electromagnetic therapy, acupuncture, cupping therapy, and apitherapy) (Cao 2015), as well as intralesional injection of steroids (Zaenglein 2016). However, the quality of evidence regarding these interventions is mixed (very low to moderate); there is no high-quality evidence at present, which prevents their widespread use in clinical practice. In recent years, with the deepening of research, some acne treatment drugs with new mechanisms of action have emerged. In 2020 the US Food and Drug Administration (FDA) approved a topical inhibitor against androgen receptors (clascoterone) as an intervention for the treatment of acne (Dhillon 2020). This drug is indicated for topical treatment of acne vulgaris in patients 12 years or above (Gold 2021). Unlike oral hormones used to treat acne, clascoterone can be applied to both male and female patients. For acne scars, various keloplasty techniques (including chemical exfoliation, laser therapy, and dermabrasion) are used clinically at present. Additionally, acupuncture, subcutaneous dissection, local subcutaneous filling, and cryotherapy can promote scar repair in acne patients (Fabbrocini 2010). Individuals with mental illness caused by acne are often treated through psychological interventions or oral antidepressant drugs. An effective acne treatment regimen at an early stage may be the optimal strategy for the prevention or control of associated complications (Williams 2012). According to the 'Guidelines of care for the management of acne vulgaris' published in 2016 by the American Academy of Dermatology (AAD) (Zaenglein 2016), a specific regimen for topical treatment depends on the patient's age, involved site, scope and severity of disease, and the patient's will. For topical treatment, drugs may be used alone or in combination with other drugs for topical use or oral administration. The AAD guidelines recommend the following regimens for topical treatment: benzoyl peroxide used alone or combined with erythromycin/clindamycin (for mild acne); benzoyl peroxide combined with retinoids or oral antibiotics (for moderate to severe acne); and retinoids used alone or combined with topical/oral antibiotics (for patients with inflammatory acne lesions). In addition, adapalene, azelaic acid, dapsone, sulfur, nicotinamide, resorcinol, aluminum chloride, and zinc may be used for acne treatment. Guidelines released by the National Institute for Health and Care Excellence (NICE) in 2021 updated the first-line treatment regimens for acne (NICE 2021). The current guidelines recommend benzoyl peroxide for topical use combined with clindamycin for mild to moderate acne, and combined adapalene and benzoyl peroxide for topical use or azelaic acid for topical use combined with oral lymecycline/doxycycline for moderate to severe acne. Additionally, for any severity of acne, either topical adapalene combined with benzoyl peroxide or topical retinoids combined with clindamycin may be

used, but antibiotic monotherapy or topical plus oral antibiotics are not recommended.

How the intervention might work

Topical medications

As a metabolic intermediate of vitamin A in the body, retinoids affect the growth of bone and promote epithelial cell proliferation, differentiation, and keratolysis, and so on (Mukherjee 2006). Many of their tissue effects are mediated through the interaction with specific cells and nucleic acid receptors. Retinoids can correct and prevent the abnormality of biochemical composition or morphological structure of dermal connective tissue caused by harmful factors, stimulate the synthesis of skin extracellular matrix protein, accelerate the formation of new connective tissue belt in the upper dermis, and increase the tension and strength in the wound area (Griffiths 1993). Retinoic acid (Generation 1), adapalene, and tazarotene (Generation 3) are three retinoid drugs approved by the FDA for the treatment of acne (Khalil 2017). The first generation of retinoids is a natural non-aromatic compound, for which the circular structure of vitamin A is retained, but the polarity and polyene side chains are changed. The third generation of retinoids is formed through side chain cyclisation of polyene. Its structure is more rigid than that of the first generation, therefore it binds to relatively few receptors (Khalil 2017; Mukherjee 2006). Each retinoid binds to a different set of retinoid receptors: retinoic acid binds to alpha, beta, and gamma receptors, whilst adapalene and tazarotene bind selectively to beta and gamma receptors (Zaenglein 2016). Retinoids for topical use can inhibit the formation of microcomedones, reduce mature comedones, and decrease inflammatory lesions as well (Gollnick 2003a). In addition, retinoids for topical use can enhance the penetration of other topical drugs, such as antibiotics. In inflammatory acne, combinations of retinoids with antibiotics are a superior therapy to antibiotics alone (Dréno 2014; Maiti 2017). Retinoids are the core topical medication for acne treatment. Several studies have shown that retinoids for topical use can effectively relieve inflammatory or non-inflammatory lesions in acne patients; however there are adverse events associated with treatment, such as skin irritation, dry and itchy skin, peeling, and burning sensation (Kawashima 2008; Tirado-Sánchez 2013; Zakaria 2010). These adverse events can be referred to as retinoids dermatitis or retinoids reactions. The process of topical use starts with the lowest dose and frequency, which is then increased gradually with the patient's tolerance (Khalil 2017). Sunlight can aggravate the stimulation of retinoids to the skin and lead to their decomposition. Sun exposure should be avoided during the treatment process, and it is better to use at night or before going to bed (Mukherjee 2006). In addition, retinoids can be destroyed by benzoyl peroxide, therefore combination with it should be avoided (Mukherjee 2006).

Benzoyl peroxide (BPO), as a bactericidal oxidant, has mild anti-inflammatory and keratolysis effects (Strauss 2007). Due to its lipophilicity, BPO may be concentrated in the sebaceous follicles, which will result in the formation of BPO-lipid reaction products (Krakowski 2008). In addition, benzoic acid can mediate the degradation of bacterial protein through oxygen free radicals, reduce the bacterial load on the skin surface, and kill *Propionibacterium* and *Staphylococcus* for acne (Brammann 2020; Krakowski 2008; Scheer 2018). It is not limited by the mechanism of bacterial resistance, therefore it is often combined with antibiotics clinically, so as to improve the efficacy of antibiotics and inhibit the emergence of drug-resistant strains (Brammann 2020). Besides its bactericidal effect, BPO can change the cohesion of the keratinised skin layer through a keratinisation dissolution mechanism because it has a keratinisation property similar to salicylic acid (Waller 2006). After being absorbed through the skin, BPO is metabolised to benzoic acid, which is then excreted as benzoate through urination. The use of BPO is limited by its concentration, exposure to coloured substances (such as hair, fabric), and allergic contact dermatitis (Zaenglein 2016).

For individuals with mild to moderate acne, antibiotics for topical use can be appropriately selected for treatment; however, because antibiotics can easily cause resistance of *Propionibacterium* and other bacteria on the skin surface, they are mostly combined with other drugs (Katsambas 2004). The main topical antibiotics for acne include erythromycin and clindamycin, which can inhibit the growth and activity of *Propionibacterium acnes*, and have a mild anti-inflammatory effect, as well as an inhibitory effect on leukocyte chemotaxis (Leyden 2003). The efficacy of erythromycin for topical use decreases gradually with time clinically, whilst that of clindamycin is relatively stable (Simonart 2005). However, in recent years, for acne caused by *Propionibacterium*, antibacterial resistance to clindamycin has been increasing, and cross-resistance to other antibiotics has also emerged (Drucker 2012). The resistance to antibiotics may lead to failure of acne treatment and disorders of skin microbiota (Karadag 2021). According to study results (Fan 2016; Nakase 2017; Yang 2018; Zhu 2019), the proportion of antibiotics with resistance during the treatment of acne is as follows: clindamycin (30% to 55%), erythromycin (30% to 55%), doxycycline (10% to 20%), and tetracycline (10% to 20%). To avoid the emergence of multiresistant strains, topical antibiotics alone for therapy should be administered for no more than three months, or a combined therapy may be used to minimise the resistance. Alternatives to antibiotics may be used if possible (Drucker 2012; Elston 2009). The side effects of topical antibiotics are less than those of oral antibiotics, and are mainly manifested as mild skin irritation (e.g. erythema, peeling, dryness, itching, and burning sensation) (Krakowski 2008).

As an antibacterial agent, azelaic acid has antikeratinisation, antiproliferation, and anticytotoxin effects (Akhavan 2003). The pharmacological mechanism of azelaic acid for topical use may be summarised as follows:

1. inhibit and kill the bacteria in the epidermis and hair follicles (Nguyen 1995);
2. competitively inhibit the enzyme (5α-reductase)-related process for production of dihydrotestosterone, and reduce the sebum (Stamatiadis 1988);
3. inhibit the synthesis of filamentous keratin, so as to prevent hyperkeratosis (Detmar 1989);
4. inhibit cell synthesis through acting on intracellular mitochondria, thereby inhibiting cell proliferation (Fitton 1991);
5. inhibit the production and action of oxygen free radicals as an anti-inflammatory agent (Nguyen 1995).

Azelaic acid is a first-line monotherapy for inflammatory and non-inflammatory acne in adults (Dréno 2013). Its clinical efficacy is similar to that of other topical drugs for mild or moderate acne (Kainz 2016; Thielitz 2015), with high patient tolerance and satisfaction. Compared with other topical drugs for acne treatment, topical azelaic acid may cause only transient mild adverse reactions

(e.g. erythema, pruritus, scales, and burning sensation) of which the incidence rate is about 5% to 10% (Liu 2020a). The systemic blood concentration is low after it is applied, therefore it may be used by pregnant and lactating patients safely (Dréno 2013).

As an anti-inflammatory bacteriostatic agent, dapsone is a synthetic sulfone with a strong bacteriostasis effect. It interferes with the synthesis of folic acid through acting on the bacterial dihydrofolate synthase, and its mechanism of action is similar to that of sulfonamides (Geyfman 2019). Its anti-inflammatory effect is achieved by inhibiting the signal transduction induced by neutrophil myeloperoxidase and eosinophilic peroxidase, and through inhibiting hypochlorous acid production and neutrophil supplementation it may minimise inflammation associated with highly reactive oxygen species (Al-Salama 2017). After taken orally, dapsone will have a high blood concentration, which lasts a long time. It will be widely distributed in the tissues and body fluids of the whole body, thus causing serious adverse reactions (e.g. anaemia, dermatitis exfoliativa, dapsone syndrome, acute intoxication) (Piette 2008). The use of oral dapsone is therefore limited in acne treatment. Aczone (dapsone) gel 7.5% has been approved by the FDA for topical use in acne patients 12 years of age or older (Pickert 2009). Topical use may reduce a patient's systemic uptake and thus improve their tolerance. Several studies have shown that after applying 5% dapsone gel twice daily for 12 months, no systemic accumulation of dapsone occurred in patients with acne vulgaris (Lucky 2007; Thiboutot 2007). It should be noted that for patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, topical application of both trimethoprim-sulfamethoxazole and dapsone should be avoided because such a combination can cause haemolysis (Al-Salama 2017).

Salicylic acid is a fat-soluble organic acid. It is often used in the treatment of acne for antifungus resistance and keratinolysis (Akarsu 2012). In addition, a low concentration of salicylic acid (0.5% to 3.0%) is often added to cleansers, Choi 2010, creams, Zheng 2013, and lotions, Babayeva 2011, as an over-the-counter treatment regimen for acne (Liu 2020a), whilst a high concentration of salicylic acid may exfoliate the acne chemically through its strong keratinisation effect (Bae 2013). Salicylic acid, with its lipophilicity, can decompose the follicular keratotic plugging hair through the keratinolysis effect, and achieve desquamation through dissolving gelatinous substance between the stratum corneum cells (Akarsu 2012; Leyden 2003). Due to the degradation and anti-inflammatory properties of salicylic acid, its topical use can alleviate inflammatory or non-inflammatory acne symptoms (Bowe 2008; Thiboutot 2009). Salicylic acid of concentration 2% or higher can cause skin peeling or skin irritation (e.g. burning sensation). A concentration of 3% to 6% is commonly used for the treatment of skin diseases for hyperkeratosis, such as psoriasis and ichthyosis. Salicylic acid of concentration 5% to 40% is used to remove warts and corns (Bowe 2008). Salicylic acid is a type C drug for pregnancy approved by the FDA (Kempiak 2008). Given the limited number of studies, the safety of salicylic acid in lactating patients is still unclear. However, it has been approved for the treatment of acne in children (Akhavan 2003).

Nicotinamide (also called niacinamide) is an amide compound of nicotinic acid with anti-inflammatory effect on acne (Shalita 1995). It may also inhibit sebum (Forbat 2017). Nicotinamide is a form of vitamin B_3 that comes primarily from the diet in the body. Nicotinamide deficiency may cause pellagra, which is characterised by diarrhoea, dermatitis, and dementia clinically (Rolfe 2014). Topical application of nicotinamide may help to form a skin barrier and prevent infection through an antibacterial effect against acne (Wohlrab 2014). In addition, it has an anti-inflammatory effect because it may reduce the secretion of IL-8 in vitro and inhibit the chemotaxis of leukocytes (Grange 2009). Nicotinamide may also inhibit the release of lysosomal enzymes and degranulation of mast cells, thus enhancing its anti-inflammatory effect (Wohlrab 2014). Several studies have shown that topical application of nicotinamide can reduce sebum on the skin surface of acne patients (Draelos 2006; Khodaeiani 2013; Walocko 2017). Nicotinamide has a low risk of side effects, and only mild skin irritation may occur with topical use. It may be used safely in women during pregnancy (Rolfe 2014).

Alpha-hydroxy acids are a family of organic acids derived from natural fruits (Hunt 1992), including glycolic acid, lactic acid, malic acid, tartaric acid, and citric acid, which are often used in cosmetic formulas (Tang 2018). Low concentrations (less than 10%) of alpha-hydroxy acids may interfere with the formation of ionic bonds, thus reducing the cohesion between epidermal keratinocytes, and removing aged keratins (Van Scott 1984). The acid breaks down the stratum corneum that accumulates on the skin through dissolving the adhesions between the upper cells of the skin (Hunt 1992). One of the causes of acne formation is the accumulation of keratins, which leads to the blockage of pilosebaceous orifice, which in turn makes the sebaceous glands unable to excrete sebum smoothly. At a low concentration, alpha-hydroxy acids can induce the peeling of dry scales on the skin surface and reduce the adhesion of follicular keratinocytes (Kaminsky 2003), thus preventing the formation of acne. High concentrations of alpha-hydroxy acids (more than 30%) have strong penetrating power and can exfoliate to achieve the effect of chemical peeling (Sharad 2013). As a peeling agent, their peeling effect is mild, and pigmentation or scar formation is not expected (Tung 2000).

After sulphur comes into contact with skin and tissue, sulphide is generated under the action of its secretion, which has bactericidal and antikeratinisation effects (Gupta 2004). Sulphur-containing preparations with a concentration of 1% to 10% for topical use are useful in the treatment of acne (Akhavan 2003). Sulphur mostly exists in the form of soap, emulsion, ointment, and foam (Liu 2020a). In the treatment process, sulphur is mostly combined with benzoyl peroxide or sodium sulfacetamide (Del Rosso 2009; Liu 2020b; Wilkinson 1966). Its treatment for acne may be realised through the antikeratinisation effect of sulphur and the inhibition of acne proliferation. The possibility of side effects caused by topical application of sulphur is extremely small. As FDA pregnancy category C drugs, the most common adverse reactions are dry skin or pruritus (Gupta 2004). However, given the lack of research on sulphur content in breast milk excretion, it should be used cautiously by women in lactation (Akhavan 2003).

Zinc, as one of the trace elements essential to the human body, is very important for the development and immunity of the body. Serum zinc level is considered to be related to the severity and typing of acne lesions (Rostami 2014). The anti-inflammatory and antibacterial effects of zinc are possible mechanisms of action against acne (Liu 2020a). Zinc maintains the immune response through protecting the function of macrophages and neutrophils, and stimulating the activity of natural killer cells and complement (Cervantes 2018). One study showed that zinc can effectively inhibit

the activity of *Propionibacterium acnes* in vitro (Fluhr 1999). In addition, zinc inhibits the production of inflammatory mediators, such as IL-6 and TNF-α, thus exerting its anti-inflammatory effect (Cervantes 2018; Sandeep 2014). Zinc is combined with antibiotics for the treatment of acne clinically. For example, 1% clindamycin + zinc gel can alleviate inflammatory and non-inflammatory lesions gradually, significantly reduce *Propionibacterium acnes* and *Micrococcus* on the skin surface, whilst in the process few drug-resistant strains appear (Cunliffe 2005). There are no reported serious adverse reactions induced by the topical use of zinc, and application site reactions (such as itching) were always mild and transient (Cunliffe 2005; Liu 2020b; Sharquie 2008).

Clascoterone is an inhibitor against androgen receptors used for treating androgen-dependent skin diseases, including androgen alopecia and acne vulgaris (Dhillon 2020). The relevant mechanism of action for treating acne vulgaris remains unclear (Dhillon 2020). Studies have shown that clascoterone may compete with dihydrotestosterone, Alkhodaidi 2021, and achieve high-affinity binding with androgen receptors in hair follicles and sebaceous glands (Rosette 2019b), to reduce the signal transmission required for the development of acne and antagonise the production of androgen-regulated lipids and inflammatory cytokines (Rosette 2019a). Study results suggest that the treatment of acne vulgaris by clascoterone may improve the success rate for investigator's global assessment and reduce the non-inflammatory lesion counts effectively (Alkhodaidi 2021). Clascoterone has certain efficacy and safety in the treatment of acne vulgaris (Alkhodaidi 2021; Hebert 2020). After applied externally, clascoterone may be metabolised into corticosterone rapidly. As an inactive metabolite, corticosterone has a low probability for adverse events like systemic absorption and systemic androgen resistance (Alkhodaidi 2021). Adverse reactions associated with clascoterone include local skin irritation (e.g. erythema, itching, desquamation, and burning; Mazzetti 2019a; Mazzetti 2019b) and potential hypothalamic-pituitary-adrenal axis inhibition (Eichenfield 2020; Mazzetti 2019a).

Physical therapy

Radiofrequency therapy has been gradually introduced into the field of dermatosis in recent years. As a high-frequency electromagnetic wave, radiofrequency has a micro-cauterisation effect that promotes re-epithelialisation of skin, as well as the regeneration and remodelling of dermal fibroblasts (Lan 2018; Simmons 2016). Radiofrequency can be divided into unidirectional/unipolar, bipolar, and fractional radiofrequencies depending on the electrode configuration. A unipolar radiofrequency device can send electrical energy deep into the dermis, whilst high controllability bipolar radiofrequency can alleviate pain more effectively, but is limited in penetration. Fractional radiofrequency dissipates energy from multiple electrodes, thus further alleviating patient discomfort during the operation (Simmons 2016). Radiofrequency therapy is widely used to treat moderate to severe acne or acne scars, but it seems to be more suitable for patients with dark skin tones (Zhang 2013). Most patients with moderate to severe acne reportedly respond well to radiofrequency therapy without any acne medication (Ruiz-Esparza 2003). Radiofrequency can reduce inflammation around follicles and reduce the area of sebaceous gland (Prieto 2005), which may help explain its usefulness in acne treatment. Radiofrequency therapy may treat moderate to severe acne safely and effectively. In addition, a 16-week prospective clinical study showed that radiofrequency therapy can reduce the grade of acne scar effectively, and pathological and immunohistochemical results have verified the therapy as a feasible treatment option (Kwon 2017).

Photodynamic therapy is based on the interaction of light, photosensitiser, and oxygen (Fritsch 1998; Sakamoto 2010a). It may cause functional or morphological changes in cells and biomolecules through the action of light with the participation of photosensitiser and oxygen, also known as photosensitisation-oxidation action (Zhang 2020). Acne caused by *Propionibacterium acnes* may produce endogenous porphyrin, which may produce highly reactive singlet oxygen after absorption of light rays, thus destroying the bacteria (Mariwalla 2005). Blue light is most often used as the logical wavelength in clinical practice for the treatment of acne because porphyrin mostly absorbs blue light (Mariwalla 2005; Ross 2005). Red light may also be absorbed by porphyrin, thus penetrating deep into the skin and affecting inflammatory mediators (Ross 2005). The study of photosensitisers is the key to the future of photodynamic therapy. As a special chemical, photosensitisers may transfer energy. 5-aminolevulinic acid (5-ALA), an endogenous 5-carbon compound, and its methyl ester derivative (MAL), can aggregate to sebaceous glands and convert to protoporphyrin IX after being applied externally as a photosensitiser (Lee 2020; Zhang 2020). Exposure to a specific wavelength of light can lead to reversible damage to the sebaceous glands, thus relieving moderate to severe acne (Del Duca 2019; Sakamoto 2010b). Low-dose photodynamic therapy (low-dose photosensitiser, low light intensity, shortened time between the photosensitiser and light, low penetration of blue light, and/or various pulse sources of irradiation) has a temporary antibacterial or immunomodulatory effect, whilst high-dose photodynamic therapy (high-dose photosensitiser and high flux red light) treats the disease through damage to the sebaceous glands (Sakamoto 2010a). Photodynamic therapy has been widely used in the treatment of many diseases due to its low toxicity, low trauma, and low recurrence rate.

In laser therapy, the relevant mechanism of action is to apply heat to destroy the target tissues selectively and stimulate dermal fibroblasts to replace collagen and elastin (Schoenberg 2019; Sobanko 2012). The short wavelength laser acts on the epidermis, superficial dermis, and vascular components, whilst the long wavelength laser acts on the sebaceous glands (Alexiades 2017). Pulsed dye laser (PDL), a laser used specifically for the treatment of vascular lesions (Erceg 2013), may achieve targeted damage on a specific structure in the skin without damaging surrounding tissues, based on the principle of selective light radiation absorption by different tissues (Anderson 1983; Erceg 2013). Studies have shown that healthy individuals may develop acute skin inflammation (neutrophils, monocytes, and mast cells may be observed outside the dermal vessels) after receiving PDL (Omi 2005). A large number of lymphocytes and fibroblasts may be observed four weeks after treatment, and the number increases over time. PDL may affect the skin by direct activation of skin immunity (Omi 2005). Adverse reactions associated with PDL, mainly erythema, oedema, purpura, scab, pigmentation, and scarring (Levine 1995), depend on the selected parameters, location, and skin type of the patient (Erceg 2013).

Keloplasty

Keloplasty involves the use of laser or chemicals to destroy skin scars, and then promote the generation of new normal tissues to achieve the effect of treating scars. Scar revision mainly includes

laser therapy, chemical peeling, and dermabrasion. Laser therapy remodels and re-epithelialises collagen by cauterising the surface to remove the epidermis and part of the dermis of scar (Abdel Hay 2016). It usually needs to be performed only once, but side effects such as persistent erythema, pigmentation, and infection may occur (Abdel Hay 2016). Chemical peeling is the use of high concentrations of chemical drugs (such as alpha hydroxy acid, glycolic acid, phenol, trichloroacetic acid, etc.) to destroy the connection between stratum corneum cells (Abdel Hay 2016); promote epidermis abscission and collagen production; and help elastic fibre renewal and substrate formation. Chemical peeling can cause serious skin irritation and is associated with frequent adverse reactions, and excessive absorption of phenolic chemicals may increase the risk of cardiac toxicity (Landau 2007), therefore it is recommended that high-concentration chemical skin replacement be completed by medical professionals. Dermabrasion is the process of removing epidermis or part of epidermis and dermis with tools such as high-speed brushes and diamond rollers, which can accurately locate the edge of scar, but it can cause pain, pigmentation, and other adverse reactions (Abdel Hay 2016).

Complementary therapy

Complementary and alternative medicine (CAM) is a form of therapy that is often used in addition to conventional treatment methods (Cao 2015). CAM may be divided into traditional and folk remedies (e.g. Traditional Chinese Medicine (TCM), homeopathy, Indian medicine, and Indian Ayurveda), bio-electromagnetic therapy (e.g. electromagnetism and electroacupuncture), physical and mental intervention therapy (e.g. meditation, hypnosis, and psychotherapy), diet and nutrition (anti-acidification food group, immunoreactive foods, immune activation, health maintenance, and food therapy), biological therapy (apitherapy, shark chondroitin, and chelation therapy), manual therapy (TCM massage, massage, touch therapy, and acupuncture), herbs, aromatherapy, physical therapy, hot spring therapy, and oxygen therapy. CAM is an important healthcare component. Although many CAM therapies are only used in the corresponding countries of origin, some of them reported by relevant studies (such as physical therapy (Zeng 2020), and diet and nutrition (Penso 2020; Smith 2007)) have gained wide acceptance.

Traditional Chinese Medicine is a unique theoretical system formed gradually under the guidance of ancient materialist dialectics. The discipline includes herbs, acupuncture, TCM massage, cupping, and exercise therapy (e.g. Tai chi and Qigong). According to TCM theory, the occurrence of acne is mostly related to *Lung Channel of Hand-Taiyin* (LU) and/or *Stomach Meridian of Foot-Yangming* (ST) heat, damp-heat accumulation, phlegm-dampness condensation, and *Qi* (a primary substance in the human body maintaining life activities in TCM theory) and *Blood* stasis (Kou 2020). In TCM herbs (e.g. forsythia, honeysuckle, dandelion, coix seed, rhubarb, and *Angelica dahurica*) are used for regulating *Qi*, activating *Blood*, clearing damp, and relieving heat, so as to alleviate acne (Chen 2016). In addition, one study has shown that blood pricking and cupping at *Dazhui point* (GV 14) may improve the skin lesions of individuals with moderate acne vulgaris (Xu 2013). Acupuncture may co-ordinate the secretion of androgen in patients, thus inhibiting the excessive secretion of sebaceous glands, whilst promoting local blood circulation and the activity of sebaceous glands, thereby normalising local follicular secretion of hair-follicle sebaceous glands (Li 2009). TCM can also be used to treat mental health problems caused by acne. In TCM theory, mental health problems are related to *Heart meridian of Hand-Shaoyin* (HT), *Gallbladder meridian of Foot-Shaoyang* (GB), and *Liver meridian of Foot-Jueyin* (LR), which should be targeted by interventions to regulate the emotions, thereby avoiding the adverse consequences of an emotional imbalance.

In recent years, more attention has been paid to the diet of acne patients. Although genetic factors and hormone levels play a greater role in acne than eating habits (Magin 2005), diet may still increase the risk of acne as a regulator of gene expression (Cao 2015). Studies have shown that acne is more likely to occur amongst people ingesting sweets, fresh fruit juice, chocolate, and greasy foods (El-Akawi 2006; Law 2010). The influence of dairy and soy products on acne is controversial, with some studies showing an association with the incidence of acne (Spencer 2009), and others finding no association (Law 2010). The efficacy and safety of other CAM therapies in the treatment of acne are still unclear due to lack of evidence, but the commonly used CAM therapies aim to reduce local inflammatory response, kill pathogenic bacteria on the skin surface, and reduce the secretion of hair-follicle sebaceous glands (Cao 2015).

Why it is important to do this overview

The title of this overview of systematic reviews was prioritised by Cochrane Skin in their 2020 prioritisation exercise, which aimed to identify the most important systematic review titles within the group's scope (Cochrane Skin 2020). Another overview of systematic reviews focusing on systemic interventions for acne is also being produced (Costa 2021). Although some reviews have compared the effectiveness of different oral drugs head-to-head (Arowojolu 2012; Costa 2018; Walsh 2016), there is no comprehensive evidence summarising the available data on non-pharmaceutical therapies or topical drugs; in particular, the horizontal comparison amongst the non-systemic pharmacological interventions is still lacking at present. It is therefore necessary to use an evidence-based medicine approach to summarise the existing evidence of non-systemic pharmacological interventions for acne. An overview is the best means to summarise the evidence of existing systematic reviews. The results will also provide decision-makers with the latest and most comprehensive evidence in the field, so as to support decision-making and the development of relevant guidelines.

OBJECTIVES

To synthesise the existing evidence on the efficacy and safety of non-systemic pharmacological interventions in the treatment of acne vulgaris and related skin complications.

METHODS

Criteria for considering reviews for inclusion

Types of studies

We will include systematic reviews (Cochrane and non-Cochrane) of non-systemic pharmacological treatments for acne vulgaris. We will exclude reviews rated as high risk of bias using the ROBIS tool (see Assessment of methodological quality of included reviews).

We will only include data from randomised controlled trials (RCTs).

We will include all non-overlapping systematic reviews. However, for groups of overlapping reviews, we will primarily include the latest Cochrane Review unless there is a more recent high-quality non-Cochrane Review. Where there is no Cochrane Review, we will include the highest-quality, most relevant, or most comprehensive systematic review.

Types of participants

Participants with a diagnosis of mild, moderate, or severe acne vulgaris, defined by any classification system or healthcare professional. We will include individuals regardless of gender, age, ethnicity, or healthcare setting. We will also include acne patients with skin complications, such as scars, including scars of any severity caused by acne, such as hypertrophic scars, atrophic scars, and keloids.

If a systematic review considered other types of acne as well as acne vulgaris, we will include the review and analyse only the data from RCTs addressing acne vulgaris.

Types of interventions

Eligible interventions will include topical medications (including tretinoin, antibiotics, benzoyl peroxide, azelaic acid, etc.) and all non-pharmacological interventions, including physical therapy (e.g. laser therapy, radiofrequency, light therapy, etc.) and complementary therapy (e.g. diet and nutrition, mind-body interventions, bioelectromagnetics, traditional and folk remedies, biological treatments, manual healing methods, herbal medicine, etc.). Interventions may be used alone or in combination. We will also include complementary topical treatments.

The comparators may be any of the following: placebo, no treatment, usual care, other topical medications, or other non-pharmacological, non-systemic interventions.

Types of outcome measures

The included reviews should include at least one of the outcomes listed below; however, we will include reviews that aimed to report at least one of the outcomes listed but found no data.

Primary outcomes

1. Improvement in acne severity as assessed by a decrease in total lesion counts and inflammatory and non-inflammatory lesion counts (if counted separately).
2. Frequency of participants experiencing at least one serious adverse event (defined as that associated with death, hospitalisation, foetal losses, miscarriage, malformation, or permanent disability, in accordance with FDA 2021).

Secondary outcomes

1. Improvement in acne severity as assessed by participant's global self-assessment using a Likert-type scale. This will include improvement in acne scar severity where relevant.
2. Improvement in acne severity as assessed by an investigator's global assessment using a Likert-type scale or a previously published subjective grading system. This will include improvement in acne scar severity where relevant.
3. Quality of life measured by any specific or generic validated tool.
4. Frequency of participants experiencing at least one less serious adverse event. We intend to analyse frequency of serious and less serious adverse events only as reported in the included reviews.

These efficacy outcomes are currently the most frequently adopted in acne clinical trials (Thiboutot 2019), according to the work of the Acne Core Outcomes Research Network (ACORN).

Timing

Considering the effect of intervention time on efficacy, we will divide the intervention time into two stages: short-term intervention stage (up to 12 weeks) and long-term intervention stage (more than 12 weeks). If there is more than one time point for follow-up in a phase, we will select the final time point for evaluation.

Search methods for identification of reviews

We aim to identify all relevant systematic reviews regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist will search the following databases for relevant systematic reviews with no restriction by date:

- the Cochrane Database of Systematic Reviews (CDSR) in the Cochrane Library;
- MEDLINE via Ovid (from 1946 onwards);
- Embase via Ovid (from 1974 onwards);
- Epistemonikos (www.epistemonikos.org/en/).

We will use terms for acne to search CDSR (see Appendix 1) and Epistemonikos (see Appendix 2). We will use filters developed for identifying systematic reviews by the Scottish Intercollegiate Guidelines Network (SIGN) with acne terms to search MEDLINE (see Appendix 3) and Embase (see Appendix 4).

Searching other resources

Searching reference lists

We will check the bibliographies of systematic reviews selected for inclusion to identify further references to relevant reviews.

Correspondence with experts

We will contact original authors for clarification and further data if review data as needed.

Errata and retractions

The Cochrane Skin Information Specialist will run a specific search to identify errata or retractions related to our included reviews, and we will examine any relevant retraction statements and errata that are retrieved.

Data collection and analysis

The methodology for data collection and analysis is based on Chapter V of the *Cochrane Handbook of Systematic Reviews of Interventions* (Pollock 2021).

Selection of reviews

Two overview authors (YY and YYW) will independently screen the retrieved articles against the inclusion criteria. We will obtain the full texts of reviews meeting these criteria and screen them again to confirm inclusion. Any differences will be resolved through discussion or consultation with a third party (HJC). During the title and abstract screening stage, all systematic reviews will be included regardless of methodological quality. During the full-text screening stage, systematic reviews which are judged to be at high risk of bias according to the ROBIS tool will be excluded (see Assessment of methodological quality of included reviews). We will primarily include Cochrane Reviews, but will additionally include non-Cochrane systematic reviews when a Cochrane Review of a specific systemic intervention for acne was published before 2015, or no relevant Cochrane Reviews are available. We will consider including more than one review on a topic if no single eligible review covers all the relevant literature.

Data extraction and management

We plan to include a table in the overview which maps the primary RCTs contained within the included systematic reviews to show any overlap between different reviews (see Table 1).

We will use a standardised data extraction form to extract the following information from each included systematic review.

- Basic information, such as title, author, publication date, search date, search method, number of RCTs included, number of participants included.
- Criteria for inclusion of population, such as restrictions on demographic data, diagnostic criteria for disease; age; gender; ethnicity; severity of disease.
- Details of interventions and comparators, such as dose, duration of treatment, and co-interventions.
- Estimates of effects: predefined primary and secondary outcomes, effect size (odds ratio (OR) or risk ratio (RR), mean difference (MD) or standardised mean difference (SMD) with 95% confidence interval (CI), I^2 value) of the comparison(s) in meta-analysis where possible.
- Subgroup analysis and relevant data.
- Information on conflicts of interest and funding sources (including relevant information for the included reviews and whether to consider relevant information for the original RCTs).
- The methodological quality of the RCTs included in the review (i.e. risk of bias, as assessed with any validated tools).
- Quality of evidence (GRADE assessment).

Two overview authors will independently extract and cross-check data (YY and YYW), with any differences being resolved by a third party (HJC). In the case of inaccuracy or ambiguity of information concerning the included systematic reviews, we will contact the corresponding authors via email to obtain the needed information. We will not re-extract information from the original RCTs.

We will enter data into Cochrane Review Manager 5 software (Review Manager 2020).

Assessment of methodological quality of included reviews

Quality of the included reviews

We will analyse each included review to determine to what degree it satisfies the criteria specified in the ROBIS tool, which assesses the risk of bias in a systematic review (Whiting 2016). The tool is completed in three phases: 1) assess relevance (optional), 2) identify concerns with the review process, 3) judge risk of bias. Phase 2 includes four domains: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings. Each domain has five or six signalling questions which can be answered with 'yes', 'probably yes', 'probably no', 'no', or 'no information', with 'yes' indicating low concerns. We will then judge the level of concern for each domain as 'low', 'high', or 'unclear'. If the answers to all signalling questions are 'yes' or 'probably yes', then the level of concern can be judged as low. However, if any of the signalling questions are answered with 'no' or 'probably no', then there is potential concern about the existence of bias. Phase 3 of the tool considers whether the systematic review is at risk of bias overall. In this phase, the overview author needs to summarise any concerns from the four domains in phase 2, and then answer three signalling questions. As in phase 2, if these signalling questions are answered with 'yes' or 'probably yes', then the overall risk of bias can be judged as low. If one or more signalling questions are answered with 'no' or 'probably no', then the overall risk of bias is likely to be high. Two overview authors (YY and YYW) will independently apply all items of the ROBIS tool to each of the selected reviews. A third-party author (HJC) will resolve any disagreements during the collection and management of data. We will present the results of the assessments in tabular and graphic format.

Risk of bias of primary studies included in reviews

We will extract and report the risk of bias assessments, irrespective of the evaluation tools employed by the included reviews (such as Cochrane risk of bias tool, Jadad scale, etc.).

Quality of evidence in the included reviews

We will extract GRADE assessments where these are available. If GRADE assessments were not conducted, we will conduct them using the recommendations provided in Chapter V of the *Cochrane Handbook for Systematic Reviews of Interventions,* Pollock 2021, and related literature (Meader 2014).

Data synthesis

Summary of findings and assessment of the certainty of the evidence

We will present summary of findings tables for the primary and secondary outcomes, which will include the following clinically important comparisons.

1. Benzyl peroxide versus placebo or no treatment
2. Topical antibiotics versus placebo or no treatment
3. Topical retinoids versus placebo or no treatment
4. Benzyl peroxide versus topical retinoids
5. Benzyl peroxide versus topical antibiotics
6. Topical retinoids versus topical antibiotics

Where suitable data are available, we may consider evaluating other clinically relevant combination treatments as described

in the National Institute for Health and Care Excellence (NICE) guidance (NICE 2021).

Besides the descriptive summary of the results of each included review, we will conduct evidence mapping, and present the results using bubble plot. Each bubble represents a pooled summary effect from a systematic review. The x-axis, representing treatment effect, is marked as 'Large, important effect', 'Moderate, may not be important effect', 'Trivial, small unimportant effect', 'Unclear evidence of harm', and 'Clear evidence of harm' (Schünemann 2021), and reviews plot accordingly as indicated by the pooled estimate of effect of the individual reviews. The y-axis, representing quality of evidence, is marked as 'High certainty of the evidence', 'Moderate certainty of the evidence', 'Low certainty of the evidence', and 'Very low certainty of the evidence' (Schünemann 2021), and reviews plotted accordingly as indicated by the results of the GRADE assessment. The bubble size represents the number of participants involved in each pooled analysis of a systematic review, and the colour of the bubbles represents different interventions. After summation and analysis, we will follow the guidance for phrasing conclusions in Chapter 15 of the *Cochrane Handbook* and report our conclusions in the form of a 'summary of results' table (Schünemann 2021).

Subgroup analyses

We will conduct the following subgroup analyses, if data permit:

- severity of acne (e.g. mild, moderate or severe);
- age (e.g. children, adolescents, middle-aged, or elderly patients);
- ethnicity (e.g. Asian, black, white);
- gender.

For our subgroup analysis, we may merge and re-analyse the subgroups included in the systematic reviews. We will perform analysis based on the information described by the author and the data and results in meta-analysis, instead of re-extracting and analysing the original RCTs. We will use Review Manager 5 software (Review Manager 2020). For dichotomous outcomes, we will calculate RR as the effect sizes and use the Mantel-Haenszel random-effects method for the analysis. For continuous outcomes, we will use MD if the results are presented using the same scale/instrument, or SMD if different scales/instruments are used, employing the inverse-variance random-effects method for analysis. The performance test is 0.05 (Deeks 2021). For all re-analysed results, we will produce forest plots and report heterogeneity (including I^2 statistic, P value). We will use the following I^2 thresholds:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We acknowledge that the I^2 statistic depends on both the magnitude and direction of effects and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test) (Deeks 2021). We will report the impact of clinical and statistical heterogeneity when discussing the results of the analyses.

If possible, we will compare the results reported by the included reviews to any minimal clinically important differences (MCID) reported in the literature.

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ADDITIONAL TABLES

Table 1. Template for a table mapping the primary randomised controlled trials (RCTs) contained within included systematic reviews

	Review 1	Review 2	Review 3	[...]	Review 'k'
Primary RCT 1	Yes/No/Related note[a]	Yes/No/Related note	Yes/No/Related note	[...]	Yes/No/Related note
Primary RCT 2	Yes/No/Related note	Yes/No/Related note	Yes/No/Related note	[...]	Yes/No/Related note
[...]	[...]	[...]	[...]	[...]	[...]
Primary RCT 'i'	Yes/No/Related note	Yes/No/Related note	Yes/No/Related note	[...]	Yes/No/Related note

[a]Mark 'Yes', 'No', or 'Related' note in each cell. The purpose is to observe which original RCTs are included in each included review in order to determine whether different reviews include the same RCTs.

APPENDICES

Appendix 1. Search strategy for the Cochrane Database of Systematic Reviews (the Cochrane Library)

#1 MeSH descriptor: [Acne Vulgaris] explode all trees
#2 acne:ti,ab
#3 #1 or #2

Appendix 2. Search strategy for Epistemonikos

We will use the Advanced Search facility. We will search for the term 'acne' in the title or abstract of a record, and limit results to Publication type 'systematic review' and Systematic Review Question 'interventions'.

Appendix 3. Search strategy for MEDLINE (Ovid)

1. exp Acne Vulgaris/
2. acne.ti,ab.
3. 1 or 2
4. meta analy$.tw.
5. metaanaly$.tw.
6. (systematic adj (review$1 or overview$1)).tw.
7. exp "Review Literature as Topic"/
8. Meta-Analysis as Topic/
9. Meta-Analysis/
10. systematic review.pt.
11. or/4-10

12. cochrane.ab.
13. embase.ab.
14. (psychlit or psyclit).ab.
15. (psychinfo or psycinfo).ab.
16. (cinhal or cinahl).ab.
17. science citation index.ab.
18. bids.ab.
19. cancerlit.ab.
20. or/12-19
21. reference list$.ab.
22. bibliograph$.ab.
23. hand-search$.ab.
24. relevant journals.ab.
25. manual search$.ab.
26. or/21-25
27. selection criteria.ab.
28. data extraction.ab.
29. 27 or 28
30. "Review"/
31. 29 and 30
32. Comment/
33. Letter/
34. Editorial/
35. Animals/
36. Humans/
37. 35 not (35 and 36)
38. or/32-34,37
39. 11 or 20 or 26 or 31
40. 39 not 38
41. 3 and 40

Lines 4-39: search filter designed by the Scottish Intercollegiate Guidelines Network (SIGN) to retrieve systematic reviews. The filter is available at www.sign.ac.uk/what-we-do/methodology/search-filters/. Line 10 added by the Cochrane Skin Information Specialist - this publication type became available after the filter was designed.

Appendix 4. Search strategy for Embase (Ovid)

1. exp acne vulgaris/
2. acne.ti,ab.
3. 1 or 2
4. exp meta analysis/
5. ((meta adj analy$) or metaanalys$).tw.
6. (systematic adj (review$1 or overview$1)).tw.
7. or/4-6
8. cancerlit.ab.
9. cochrane.ab.
10. embase.ab.
11. (psychlit or psyclit).ab.
12. (psychinfo or psycinfo).ab.
13. (cinahl or cinhal).ab.
14. science citation index.ab.
15. bids.ab.
16. or/8-15
17. reference lists.ab.
18. bibliograph$.ab.
19. hand-search$.ab.
20. manual search$.ab.
21. relevant journals.ab.
22. or/17-21
23. data extraction.ab.
24. selection criteria.ab.
25. 23 or 24

26. review.pt.
27. 25 and 26
28. letter.pt.
29. editorial.pt.
30. animal/
31. human/
32. 30 not (30 and 31)
33. or/28-29,32
34. 7 or 16 or 22 or 27
35. 34 not 33
36. 3 and 35

Lines 4-35: search filter designed by the Scottish Intercollegiate Guidelines Network (SIGN) to retrieve systematic reviews. The filter is available at www.sign.ac.uk/what-we-do/methodology/search-filters/.

CONTRIBUTIONS OF AUTHORS

Huijuan Cao was the contact person with the editorial base.
Huijuan Cao and Yi Yuan co-ordinated the contributions from the co-authors and wrote the final draft of the protocol.
Yi Yuan, Yiying Wang, and Huijuan Cao worked on the Methods section.
Yi Yuan, Haibo Liu, and Duoduo Li drafted the clinical sections of the Background and responded to the clinical comments of the referees.
Yi Yuan, Jun Xia, Jian Ping Liu, and Hong Sang responded to the methodology and statistics comments of the referees.
Yi Yuan, Yiying Wang, Jun Xia, Haibo Liu, Jian Ping Liu, Duoduo Li, Huijuan Cao, and Hong Sang contributed to the writing of the protocol.
Ruiting Wang was the consumer co-author and checked the protocol for readability and clarity. She also ensured that the outcomes are relevant to consumers.

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DECLARATIONS OF INTEREST

Yi Yuan: declares that they have no conflict of interest.
Yiying Wang: declares that they have no conflict of interest.
Jun Xia: declares that they have no conflict of interest.
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Huijuan Cao: declares that they have no conflict of interest.
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