Red Whale
Lifelong Learning for Primary Care

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Acne

1. Acne

In 2021, NICE released guidance on the management of acne vulgaris. Here, we review its advice, alongside some useful resources from the 2018 UK Primary Care Dermatology Society guidance, a 2018 NEJM Clinical Practice article and a 2024 DTB review (NICE 2021 NG178, NEJM 2018;379:1343, PCDS 2018 acne vulgaris, DTB 2024;62:6).

This article was last updated in April 2024.

The DTB tell us why acne matters (DTB 2024;62:6):

- It is very common, affecting over 90% of teenagers and persisting into their 20s in 40–60% of patients.
- It leads to scarring in 20% of the population.
- It can cause significant distress, decreased self-confidence and

increased rates of depression and suicidal thoughts (interestingly, this occurs most frequently in women and people identifying as non-white).

1.1. Assessing your patient with acne

Ask about duration, type and distribution of lesions.

Remember:

- Acne has four contributory factors:
    - Inflammation.
    - Proliferation of *Propionibacterium acnes*.
    - Comedones (black heads and white heads) due to abnormal keratin proliferation.
    - Androgen-driven sebum production.

Consider medications which might be causing or exacerbating acne: phenytoin, lithium, steroids (including illicit anabolic steroid use) and progestogen-only contraceptives.

Acne may also be triggered by sweating, occlusive clothing and greasy topical products such as ointments.

Smoking: a dose-dependent relationship between smoking and acne severity has been demonstrated (J Invest Dermatol. 2006;126(8):1749).

Diet: NICE did not find sufficient evidence to comment on diet. A systematic review suggested that a high-dairy diet and those with 'high glycaemic loads' may be associated with more severe acne (NEJM 2018;379:1343, PCDS 2018).

Few patients will need blood tests. However, there are some features that might warrant further investigations:

- If there are features suggestive of PCOS or other endocrinopathy.
- In sudden-onset acne: consider gonadal tumours as a cause.
- Acne with systemic features such as fever arthralgia and myalgia.

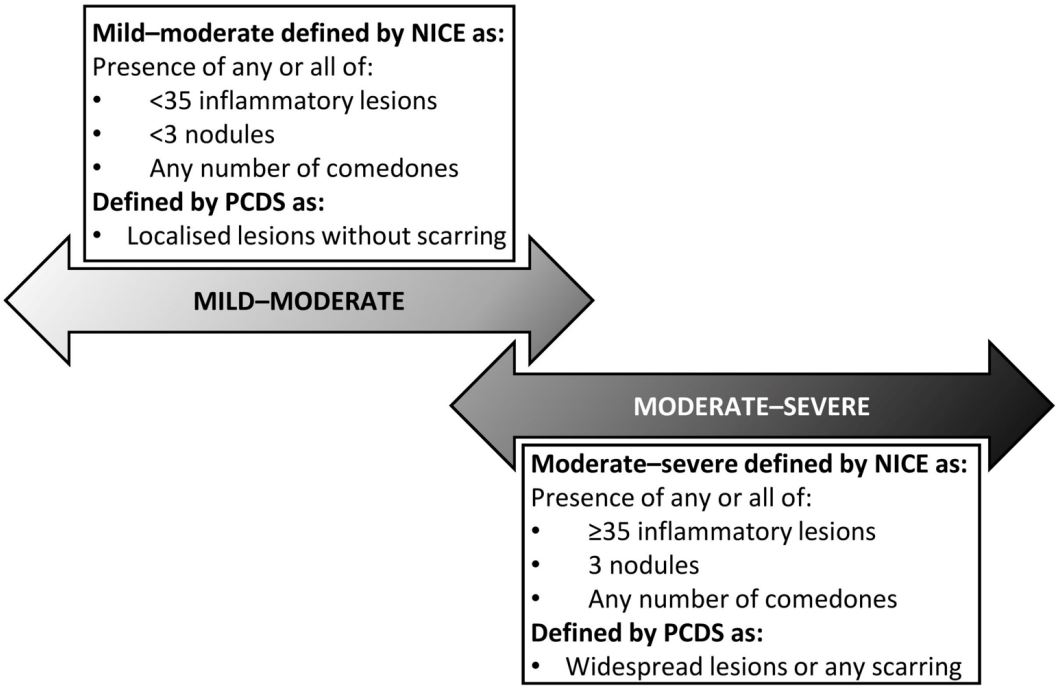
Ask about psychosocial impact. Adolescents with acne have higher levels of depression and anxiety, similar to other chronic diseases.

Treatments for acne

- All therapies for acne work on 'tomorrow's' skin; **improvement takes 3–6 weeks minimum, and may take 3–6m for maximal effect to be seen.**
- There have been very few head-to-head trials of acne treatments, and most studies have been small.
- The primary aim of treatment is to prevent or minimise scarring.

1.2. Assess severity

NICE suggests (wait for it!) *counting* the number of lesions! The Primary Care Dermatology Society (PCDS) takes a slightly more pragmatic view. Both suggest classifying the disease as mild–moderate or moderate–severe. This distinction matters because it affects treatment choices. We have summarised both approaches here:



1.3. Initial management

Information and support for patients

NICE reminds us to provide information to patients and caregivers on:

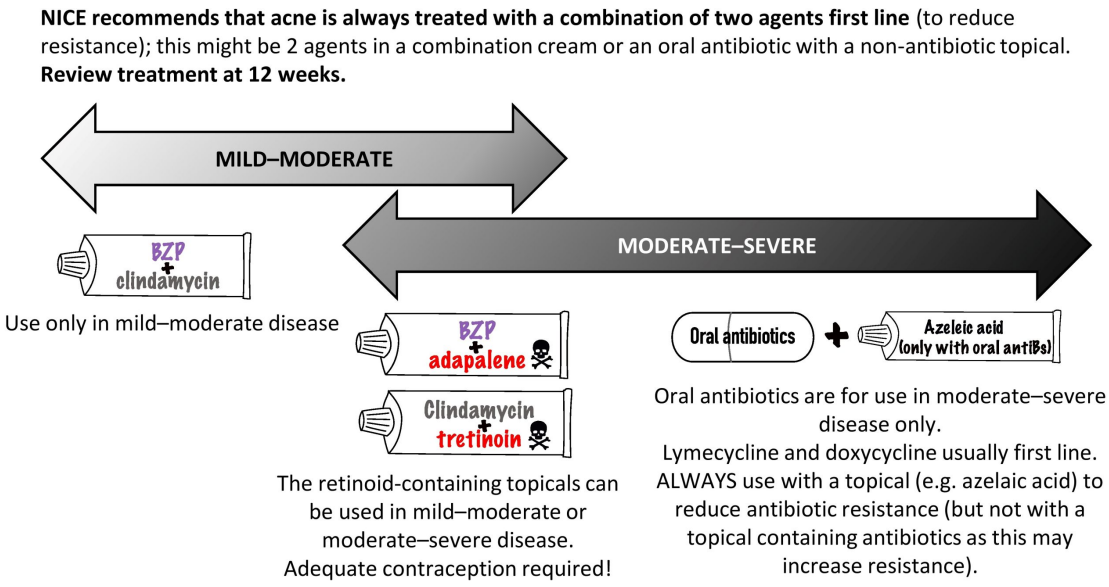
- Causes of acne (NICE does not outline any specific causes to mention but we have included a few in our introduction above).
- Treatment options, including over-the-counter treatments.
- Pros and cons of treatments:
    - Side-effects, including skin irritation.
    - Implications of treatment on pregnancy and conception.
- Importance of treatment adherence.
- Delayed onset of treatment benefits.

- Impact of acne, including psychological impact.
- Relapses after treatment: when and how to seek advice.
- Diet: NICE found no clear evidence to support any specific diet.

Skin care advice

- Avoid comedogenic make-up and moisturisers.
- Remove make-up daily.
- Avoid persistent picking at spots as this may cause scarring.
- Use a non-alkaline synthetic detergent face wash twice daily.
- *Synthetic detergent facewashes are cleansers formulated to be closer to the usual pH of skin than traditional soap. They do not produce a lather, and are less of an irritant to inflamed skin. They are widely available on supermarket shelves.*

Medication choice



Drug	Notes
TOPICALS: to reduce risk of skin irritation, initially advise either alternate-day dosing or washing off the treatment after 1h after application, and progress to usual dose (nightly application) as tolerated.	
Benzoyl peroxide (3% or 5%) with clindamycin (1%)	• Use with caution in pregnancy and breastfeeding. • Can cause photosensitivity and skin irritation. • Can bleach skin and fabrics. • **Mild–moderate disease only.**
Benzoyl peroxide (2.5%) + adapalene (0.1% or 0.3%)	• Follow MHRA advice on pregnancy prevention. • Use with caution if breastfeeding. • Can cause photosensitivity and skin irritation. • Can bleach skin and fabrics. • Can be used for **mild–moderate or moderate–severe disease.**
Clindamycin (1%) + tretinoin (0.025%)	• Follow MHRA pregnancy prevention guide. • Do not use when breastfeeding. • Can cause photosensitivity and skin irritation. • Can be used for **mild–moderate or moderate–severe disease.**

Azelaic acid (15% or 20%)	• Safe in pregnancy and breastfeeding. • **Moderate–severe disease only, alongside oral antibiotics.**
Orals	
Lymecycline 408mg or doxycycline 100mg once daily	• Do not use tetracyclines <12y or in pregnancy/breastfeeding. • Do not use topical and oral antibiotics together. • Do not use oral antibiotics without a (non-antibiotic) topical preparation.
If tetracycline not tolerated/contraindicated, consider trimethoprim or erythromycin	

1.4. Management after 12 weeks

When reviewing after 12 weeks, determine how successful the treatment has been and consider the following management options:

Review at 12 weeks	
Resolved	• Stop any antibiotic treatment; provide skin care advice. • If history of recurrent relapses, consider maintenance with topical adapalene + BzP (or monotherapy with adapalene/azelaicacid/BzP if dual therapy not tolerated).
Improving	• Repeat 12w course of current treatment but limit any topical/oral antibiotic to maximum 6m. • Consider COCP in PCOS.

Not improving	• **Mild–moderate**: try alternative. If a 12w course of 2 agents doesn't work, consider dermatology referral.
	• **Moderate–severe**: step-up treatment:
	  • If initial treatment did NOT involve antibiotics: start antibiotics.
	  • If initial treatment DID involve antibiotics: consider dermatology referral.

If PCOS likely	• If first-line treatment fails, consider adding any combined contraceptive pill (*this is NICE's advice, but the DTB suggests we can consider using combined oral contraception off-label to treat acne in any woman, not just where we suspect PCOS*). • Dianette is licensed for the management of acne in women with PCOS (see MHRA safety alert below). If used, treatment should be reviewed after 6m.

1.5. Acne complications

Complications	Actions
Acne fulminans	• Ulcerated, inflamed nodular acne with systemic illness: fever, abscesses, joint pain, loss of appetite and weight loss, enlarged liver and spleen, bleeding crusts over lesions on trunk. • Needs same-day dermatology referral for consideration of admission.
Scarring	• Advise patient to avoid picking. • Assess psychological impact. • Treat acne to avoid future scarring. • If severe scarring and persists 12m after acne has cleared, offer dermatology referral.
Relapse	• Repeat initial treatment or offer appropriate alternative. • Moderate–severe acne: consider referral. • Relapse after 2 courses oral isotretinoin should be managed by dermatology.

1.6. When to refer?

NICE suggests referral if:

- Diagnosis uncertain.
- Not responding to treatment.
- Severe nodulo-cystic acne.
- Persistent scarring or pigmentation.
- Associated mental or physical health problems (refer to relevant team).

1.7. Management in secondary care

Treatments that NICE recommends are considered in secondary care:

- Oral isotretinoin (see below for more information).
- Oral corticosteroids: may be used in acne fulminans or if severe flare occurs after starting oral isotretinoin.
- Intralesional corticosteroids: off-label triamcinolone into severe inflammatory lesions under consultant-led care only.
- Photodynamic therapy.
- Scarring may be managed with CO_2 laser treatments or glycolic peels.

1.8. Drug dilemma: when does NICE recommend using a single topical agent?

NICE suggests we should use combination (dual) agents for most. There are two situations where we might not do this:

- In mild disease where people are buying OTC preparations that are working for them (e.g. OTC benzoyl peroxide).
- Topical azelaic acid when used in combination with oral antibiotics.

- To reduce the risk of relapse in those who have recurrent relapses, if dual therapy is not tolerated (see 'resolved' in the section on 'Management after 12w' (above).

1.9. Drug dilemma: oral retinoids (isotretinoin)

Oral isotretinoin can only be prescribed under expert supervision (so not in most primary care settings).

NICE recommendations around prescribing:

- In people >12y, for severe acne resistant to first-line treatments.
- Assess mental health before starting and refer to mental health services if appropriate.
- Monitor for signs of depression during treatment.
- **Follow MHRA Pregnancy Prevention Programme (see below).**
- Continue until a cumulative dose of 120–150mg/kg is reached OR if there has been good response and no new acne lesions for 4–8 weeks, whichever is the sooner.

Drug dilemmas with retinoids	
Oral retinoids: action and effectiveness	• Effects take 1–2m to become apparent. • Most patients require a 16–24-week course. 50% of patients are permanently cured after 1 course of treatment; 20% require a second course. • Side-effects: • Highly teratogenic.

	• Chapped skin, dry eyes, epistaxis, myalgia and dysregulation of lipids and LFTs (check baseline lipids and LFTs while waiting for initial appointment) (NEJM 2018;379:1343). • Newer concerns about side-effects involving mental health and sexual function, ***which the MHRA feels we should counsel patients about pre-referral*** (see later in this table).
Retinoids and MHRA advice on pregnancy prevention	IMPORTANT SAFETY INFORMATION **For ORAL RETINOIDS** • The MHRA issued a reminder about the importance of pregnancy prevention in women taking oral retinoids; it is relevant to us in primary care because we are likely to be prescribing the contraception (Drug Safety Update 2013;6(11):H1): • Pregnancy should be excluded with a sensitive hCG test before starting retinoids. Secondary care will do or request a urine pregnancy test 3 days or less before starting treatment, and secondary care will repeat the pregnancy test every 4 weeks at appointments. • Contraception should be started 1m before starting treatment. • Women should continue contraception for: • At least 1m after completing isotretinoin or aliretinoin. • At least **2y** after completing acitretin (used for severe psoriasis). • There is no evidence that maternal exposure to semen from patients taking an oral retinoid is associated with any teratogenic effect. **What type of contraception should women on oral retinoids use?** The MHRA alert stated that "*women should be on at least one, and*

	ideally two, forms of complementary contraception, e.g. hormonal and barrier", while the BNF says "*use at least **1 highly effective** method of contraception (i.e. a user-independent form such as an intrauterine device or implant) or **2 complementary user-dependent** forms of contraception (e.g. oral contraceptives and barrier method)*". Pragmatically speaking, we take this to mean: • Offer an implant or intrauterine device or system first line. • If these are declined, use the COCP, POP or depot injection *alongside* a barrier method due to their higher failure rates. **For TOPICAL retinoids:** • Most of the SPCs say topical retinoids are contraindicated in women planning pregnancy. • While the MHRA states that systemic exposure from topical retinoids is thought to be negligible (MHRA 2019 Retinoids: risk of teratogenicity), the BNF advises that, as risk can't be excluded, females of childbearing age should use "effective contraception". According to a March 2019 Drug Safety Update, "effective contraception" includes all LARCs, the depot injection, the COCP and POP, as well as patches, vaginal rings etc., *but not* "methods used at the time of intercourse" or fertility awareness methods (gov.uk - MHRA March 2019: Medicines with teratogenic potential: what is effective contraception and how often is pregnancy testing needed?).
Isotretinoin: additional monitoring	**In October 2023, the MHRA announced additional monitoring measures for isotretinoin, including:** • 'Yellow card' all suspected adverse reactions to isotretinoin as it is a black triangle drug. • Two clinicians must agree that the prescription is necessary for patients under 18y. • Mental health and sexual function assessment, with counselling about potential side-effects in these areas, *before* starting treatment, then ongoing monitoring during therapy.

	• The MHRA feels that there is a role for primary care at the 'counselling about potential side-effects' step, stating: "we ask the referrer (usually the GP) to provide information about isotretinoin to the patient and provide counselling (where possible) regarding the benefits and risks." The British Association of Dermatology has produced a useful patient information leaflet. *What are the mental health concerns?* (Commission on Human Medicines isotretinoin expert working group report, 2023): • It's difficult to unpick any possible mental health effects of isotretinoin from the effects of living with severe acne, and several studies have shown that isotretinoin can *improve* negative mood changes caused by acne. However, there are possible associations between oral retinoids and depression, anxiety, aggression, agitation, psychosis and suicide (more on suicide in the box below). *What are the sexual function concerns?* (Commission on Human Medicines isotretinoin expert working group report, 2023): • Potential side-effects include loss of libido, erectile dysfunction and reduced genital sensation, all of which can persist long term, even after cessation of treatment.
Isotretinoin and suicide (DTB 2024;62:6)	• Older cohort studies suggested a small increased risk of suicide, although it was unclear whether this was attributable just to the drug or to the acne itself. • Newer population-based studies have ***not*** shown an increased risk of suicide, but there are reports of individual distressing cases.
Isotretinoin and LASIK eye treatment	• LASIK (laser refractive eye surgery) is contraindicated 6m before and after isotretinoin use. • This is because dry eyes can occur as a result of both isotretinoin and LASIK, and can result in corneal ulceration, infection and visual loss (BMJ 2011;342:d3353).

1.10. Drug dilemma: dapsone gel

- Dapsone is not included in NICE, European or PCDS guidelines, and is not licensed for acne in the UK.
- A common first-line agent in US guidelines (5% gel used as a twice-daily application).
- Oral dapsone is associated with risks of haemolytic anaemia, and should be prescribed by specialists.

1.11. Drug dilemma: spironolactone

A UK-based, double-blind RCT has found spironolactone beneficial in treating acne in young women (BMJ 2023;381:e074349).

400 women aged ≥18y with facial acne judged by clinicians severe enough to fit the NICE criteria for oral antibiotics were allocated to receive spironolactone or placebo. They continued any other acne treatments they were already using such as topical gels or hormonal pills.

Women were excluded if they had been using oral retinoids in the previous 6 months, if they had any plans for pregnancy in the next 6 months, or if they had contraindications to spironolactone use such as raised potassium or reduced eGFR.

Spironolactone was prescribed at a dose of 50mg daily for 6 weeks, then increased to 100mg daily.

- At 12 weeks, there was a small but statistically significant improvement

in quality-of-life scores for the women using spironolactone.

- At 24 weeks, there was improvement in quality of life and self-reported severity of acne.
- NNT to improve self-reported severity of acne at 24 weeks was 5.
- Minimal adverse reactions were reported.

In an associated editorial in the BMJ, the authors postulate that offering spironolactone to young women with acne might reduce antibiotic treatment, and could also provide an alternative where the maximum recommended 6-month course of antibiotics is complete but acne persists (BMJ 2023;381:p1114).

The author of the BMJ editorial suggests a regimen of 50mg for 2 weeks, then 100mg, i.e. stepping-up sooner than in the trial, speculating that women might gain benefit more rapidly.

Concerns about spironolactone

- Not licensed for this indication or recommended in UK guidelines.
- Cannot be used in men due to risk of gynaecomastia.
- Spironolactone cannot be used in pregnancy. The authors advise giving contraceptive counselling similar to when prescribing oral tetracyclines: for effective contraception to be in place during use and for 4 weeks after stopping treatment.
- Renal function monitoring: renal function and potassium checks are needed prior to starting treatment in all. Ongoing monitoring is only required if women are >45y of age or have other relevant comorbidities.
    - For women ≤45y and without other medications or medical history that might affect renal function, spironolactone use was

associated with very low risk of renal problems; ongoing monitoring was therefore not advised.

- Menstrual disturbance: this trial does not comment on the risk of menstrual disturbance on spironolactone, but a previous study showed menstrual irregularity only occurred at higher doses of around 200mg per day (Am. J Clin Dermatol 2017;18(2):169).

1.12. Drug dilemma: hormonal contraception

When should I offer combined oral contraception to treat acne?

NICE says we can consider adding combined oral contraception in women with PCOS if first-line treatment fails. However, the DTB suggests we could consider 'off-label' use of the COCP to treat acne in any woman.

How effective is combined oral contraception compared with oral antibiotics?

The COCP is inferior to oral antibiotics at 3 months, but equivalent to antibiotics at reducing acne at 6 months (DTB 2024;62:6).

Are some combined contraceptive pills better than others for acne?

NO! Evidence on varying effectiveness of different progestogens may have been overplayed in the past. A Cochrane review agreed and identified no differences in efficacy between different COCP preparations, including

cyproterone acetate (Dianette) (Cochrane 2012;7:CD004425). Be mindful of safety concerns for cyproterone acetate (see below), and remember that progestogen-based contraceptives may make skin worse.

Dianette

IMPORTANT SAFETY INFORMATION: cyproterone acetate with ethinylestradiol (co-cyprindiol) (Dianette)

Cyproterone acetate has been the subject of 2 MHRA safety alerts (Drug Safety Update 2013;6(11):A3 and 2020;13(11):2).

Thromboembolic risk

- Cyproterone acetate with ethinylestradiol can be used by women of reproductive age for the treatment of:
  - Androgen-sensitive skin conditions, e.g. severe acne.
  - Hirsutism.
- It should only be used when topical treatment and systemic antibiotics have failed.
- It is an effective contraceptive but should **not** be used solely as a contraceptive.
- It should not be co-prescribed with another COCP.
- The risk of VTE is low but we should remain vigilant – it is 1.5–2 times more likely to cause VTE than levonorgestrel-containing pills, but it is similar to desogestrel, gestodene and drospirenone-containing pills.

Meningioma risk

Do not use cyproterone for any indication in patients with a meningioma or a history of a meningioma.

A cumulative dose-dependent association between cyproterone acetate and meningioma has been identified.

- The risk is highest in doses of 25mg per day and above.

- A risk of meningioma has not been demonstrated with low doses used in combined contraceptives.
- Be vigilant for symptoms and signs of meningioma in patients taking cyproterone acetate (changes in vision, hearing loss, tinnitus, anosmia, postural headaches, memory loss, seizures).
- Stop treatment permanently if a meningioma is diagnosed in a patient taking cyproterone acetate.

1.13. Drug dilemma: minocycline

The DTB reminds us (DTB 2013;51:48):

- There is no role for minocycline in the treatment of acne.
- Other tetracyclines are equally effective and do not carry the same risks of SLE, autoimmune hepatitis and slate-grey skin pigmentation.

1.14. Is there *any* evidence for dietary interventions for acne?

NICE did not think so. However, many people with acne and their families ask about this. A recent JAMA review considered this issue and stated the following (JAMA 2021;326(20):2055):

- Overall, there is little high-quality evidence about the impact of particular foods on acne.
- The 'most compelling' evidence suggests that high-glycaemic-load diets may exacerbate acne.
- A number of observational studies have indicated an association (not

causation) between consumption of dairy products, particularly low-fat milk, and exacerbation of acne. A meta-analysis of these observational studies showed an OR 1.16 of acne in milk drinkers consuming ≥2 cups per day.

There have been no RCTs of dairy exclusion and impact on skin, despite the fact this would be relatively easy to do! For this reason, no standard clinical guidelines in the UK or USA offer specific recommendations on diet.

Acne

- Provide information and support, including skin care advice and advice on treatments and management of relapses.
- Use topical treatments for mild to moderate acne, and consider referring if no response after trials of 2 agents.
- Consider topical treatments + oral antibiotics in widespread moderate to severe acne, or acne with scarring.
- Beware of antimicrobial resistance with oral antibiotics – use for 12w maximum duration and always alongside topical treatments.
- Refer severe scarring acne and moderate acne that is treatment-resistant for consideration of oral retinoid treatment. Check LFT and lipid profile while waiting for appointment, and, if possible, give information on the risks and benefits at the point of referral.
- The COCP reduces sebum production and is an effective acne treatment for women with hormonal acne. There is no evidence that any particular COCP (including Dianette) is more effective – start with the one with the lowest VTE risk!

Do you still have any patients on minocycline? This could be a nice, quick safety audit for your PDP.

Useful resources:

Websites (all resources are hyperlinked for ease of use in Red Whale Knowledge)

- Acne Support
- British Skin Foundation - acne
- British Association of Dermatologists - patient information leaflet on isotretinoin

Videos

- YouTube – What is the Best Way to Treat Acne? (the DTB recommends this patient information video by Dr Mike Evans)

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