Managing Acne vulgaris – an update

# Abstract

Acne is very common and can have significant negative impact on people. Whilst sometimes a transient problem, acne may persist for many years and often leads to permanent scars or pigment changes. Guidelines unanimously advise topical treatments as first-line, although differ in recommending either topical benzoyl peroxide or topical retinoid (mainly adapalene) alone or in combination. Guidance published by the National Institute for Health and Care Excellence (NICE) advises counselling patients regarding avoidance of skin irritation when starting topical treatments and promoting adherence (treatments take 6-8 weeks to work). Oral antibiotics are currently over-prescribed for acne but have a role when co-prescribed with a non-antibiotic topical treatment. Hormonal treatments, such as the combined oral contraceptive pill, are also effective and there is growing evidence for the use of spironolactone for women with persistent acne. Recent guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) regarding isotretinoin has implications for specialist prescribing and monitoring, and increasing public awareness of potential risk of mental health problems and sexual dysfunction. Although acne is associated with psychiatric disorder, the mental health effects of isotretinoin remain controversial.

# Key messages

* Early effective treatment for acne may prevent scarring and pigment changes
* Topical treatments are first line for mild/moderate acne but patients need information on how to avoid adverse effects and that treatments take 6-8 weeks to work
* Oral antibiotics can be used as second-line treatment, or for moderate or severe acne, when co-prescribed with a non-antibiotic topical treatment
* Most guidelines suggest that duration of oral antibiotics for acne should be limited to 3 months, although NICE suggests up to 6 months
* Hormonal treatments, such as the combined oral contraceptive pill, are an alternative treatment for women but can take 3 to 6 months to work
* There is growing evidence for use of spironolactone in women with persistent acne (off-label use at present), which is also likely to take 3 to 6 months to work
* Maintenance topical treatment should be continued when discontinuing oral treatments

**Box 1 Information for patients**

|  |
| --- |
| * **NHS Health A to Z:** <https://www.nhs.uk/conditions/acne/> * **AcneSupport (British Association of Dermatologists):** <https://www.acnesupport.org.uk/> * **Youtube video from DocMikeEvans:** <https://www.youtube.com/watch?v=C5Co4czoo5s> |

# Introduction

Acne vulgaris (hereon referred to as acne) is extremely common, affecting over 90% of teenagers.1 Amongst people with acne, approximately 40-60% have acne persisting into their twenties and it leads to some degree of scarring in approximately 20% of the population.2 3 Acne can cause significant distress, decreased self-confidence and increased rates of depression and suicidal thoughts,2 particularly amongst women and people identifying as non-white.4

As well as limiting quality of life, acne makes a major contribution to antibiotic use amongst young people: long courses of oral antibiotics are common and acne accounts for the majority of antibiotic exposure amongst people aged 11 to 21 years in England.5 There is high-quality evidence supporting use of topical treatments for acne, which are recommended as first line treatment for mild-to-moderate acne.6 However, treatment adherence is low, with barriers to effective self-management including: people discontinuing treatment early due to skin irritation or not seeing early treatment effects, or not differentiating effective topical treatments from ineffective cosmetic products.7 Healthcare professionals need to promote treatment adherence by advising about delayed onset of action and how to avoid skin irritation.8 Providing information to patients is therefore crucial and NICE guidance provides a list of information that should be provided for people with acne, (see Table 1). This may be difficult to cover in brief consultations, highlighting the need for signposting towards evidence-based resources, such as those listed in Box 1.

**Table 1 Summary of information for people with acne, based on NICE guidance**

|  |  |
| --- | --- |
| Topical treatments – avoiding skin irritation | * Start with alternate-day or short-contact application (for example washing off after an hour) * If tolerated, progress to using standard application * Moisturisers may help reduce skin irritation and skin dryness – the moisturiser should be non oil-based and non-comedogenic |
| All treatments – promote treatment adherence | * Positive effects can take 6 to 8 weeks to become noticeable |
| Skin care advice | * Use a non-alkaline (skin pH neutral or slightly acidic) synthetic detergent cleansing product twice daily * Choose water based (not oil-based) and non-comedogenic preparations for skin care, make-up or sunscreen |
| Diet | * There is insufficient evidence to support specific diets for treating acne |

# Pathogenesis of acne

* Acne is primarily a condition affecting the pilosebaceous unit (hair follicles in the skin and associated oil glands), leading to inflammatory and non-inflammatory lesions and scarring,2 most commonly affecting the face but also the trunk. The aetiology remains unclear but research into dietary, hygiene or other lifestyle causes have shown these to have little influence.2 However, public perceptions around the role of diet and hygiene are linked with perceived stigma around acne.8
* Severe acne and acne scarring have a genetic component, although the specific at risk genes have not been identified.2 Therefore, asking about a family history of acne scarring, acne affecting the back, and family members requiring treatment with isotretinoin is helpful.
* Acne is associated with hyper-androgenism and is more common amongst people with polycystic ovarian syndrome, as well as rarer conditions such as adrenal hyperplasia and adrenal tumours.9
* Some medications may exacerbate acne, most importantly progesterone-only contraception, but also anabolic steroids, prednisolone, some anti-epileptics and lithium.10 Greasy topical products, such as ointments, which occlude the hair follicles, increased sweating and occlusive clothing can also trigger acne.

# Clinical features and diagnosis:

The diagnosis of acne is made on the clinical history and examination. There are no diagnostic criteria and the skin lesions seen are open comedones (whiteheads), closed comedones (blackheads), papules/nodules, cysts and scarring.11 There is no strong evidence base for different treatments for different acne subtypes (comedonal vs inflammatory), and NICE and most other guidelines provide different guidance on the basis of severity rather than subtypes.12 While classifications vary, the majority of acne is mild, with moderate or severe acne combined making up less than 15% of cases of acne.3 13 See table 2 for severity classifications and linked treatment choices.

# Treatment options and guidelines

International guidelines recommend either topical benzoyl peroxide or topical retinoid (mainly adapalene) as first line treatments, but with differences regarding prescribing products individually or as combination products.12 The NICE guideline on acne, based on systematic review and network meta-analysis comparisons of acne treatments, acknowledged uncertainty in the evidence base and recommended the options in Table 2 as first line treatments.14 15

**Table 2 Summary based on NICE guidance on first-line treatments for acne**

|  |  |
| --- | --- |
|  | **Brand names and notes** |
| **Mild to moderate acne: 12-week course of one of the following first-line options to be applied once daily in the evening** | |
| Fixed combination topical adapalene + topical benzoyl peroxide (0.1% or 0.3% adapalene + 2.5% benzoyl peroxide) | Epiduo® |
| Fixed combination topical clindamycin + topical tretinoin (1% clindamycin with 0.025% tretinoin) | Treclin® |
| Fixed combination topical benzoyl peroxide + topical clindamycin (3% or 5% benzoyl peroxide + 1% clindamycin) | Duac® |
| Topical benzoyl peroxide is an alternative if these options are contraindicated or the person wishes to avoid using a topical retinoid or an antibiotic | Acnecide®available relatively low-cost OTC |
| **For people with moderate to severe acne: 12-week course of one of the following first-line options** | |
| Fixed combination topical adapalene + topical benzoyl peroxide to be applied once daily in the evening | Epiduo® |
| Fixed combination topical tretinoin + topical clindamycin to be applied once daily in the evening | Treclin® |
| Fixed combination topical adapalene + topical benzoyl peroxide to be applied once daily in the evening, together with either oral lymecycline 408 mg or oral doxycycline 100 mg once daily | Antibiotics maximum duration 3-6 months |
| Topical azelaic acid (15% or 20%) applied twice daily, with either oral lymecycline 408 mg or oral doxycycline 100 mg once daily | Antibiotics maximum duration 3-6 months |
| Combined oral contraceptives in combination with topical agents can be considered as an alternative in women | If not contraindicated |
| Co-cyprindiol (ethinylestradiol/cyproterone acetate) products can be considered in women where other treatments have failed but require careful discussion of the risks and benefits with the patient | Careful discussion of risks and benefits. Discontinue 3 months after acne is controlled |

## Topical treatments

First line treatments for mild or moderate acne are fixed combination topical preparations containing retinoids, benzoyl peroxide or topical antibiotics, as above.16-18 It is important that patients understand that these have a delayed onset of action (6-8 weeks) and are aware of how to avoid skin irritation (Table 1).

## Oral antibiotic treatments

The NICE guideline recommends limiting oral antibiotics to 3 to 6 months, 16-18 while other guidelines suggest maximum duration 3 months in order to avoid emergence of antibiotic resistance.12 First line antibiotics are oral lymecycline or doxycycline. If these are not tolerated or are contra-indicated, the NICE guideline recommends that trimethoprim or an oral macrolide may be considered. However, clinicians report barriers to discontinuing oral antibiotics once they have been started19 including patients’ understandable concerns about acne relapse. Monotherapy with an oral antibiotic (or topical antibiotic) should not be used, because there is good evidence that antimicrobial resistance is significantly reduced by co-prescribing benzoyl peroxide.20 Consensus from clinical guidelines is that continuing topical treatments as maintenance therapy after discontinuing oral antibiotics is important in reducing the risk of relapse.12

## Hormonal treatments

Hormonal treatments are an alternative for women with acne. Except for co-cyprindiol, hormonal treatments (combined oral contraceptives or spironolactone) have an advantage over oral antibiotics and isotretinoin in that they can be continued for longer courses.

**Combined oral contraceptives**

Combined oral contraceptives (COCs) remain an option for women (‘off-label’ use in acne): although inferior to oral antibiotics at 3 months, COCs are equivalent to antibiotics at reducing acne at 6 months.21There is no firm evidence to support the use of any one COC over another in terms of acne. 22

**Co-cyprindiol (Dianette)**

Co-cyprindiol (Dianette) is licensed as a second-line treatment for women with severe acne, but is not recommended for long-term use due to safety concerns about rare, but cumulative dose-dependent, increased risk of meningioma.23

**Spironolactone for adult women**

The results of the SAFA trial, published in the BMJ in 2023, showed that oral spironolactone alongside topical treatment is effective for improving outcomes for women with persistent acne, with greater effects seen at 6 months than 3 months.24 25 Spironolactone was well-tolerated starting at a dose of 50mg increasing to 100mg per day,24 although higher doses can be associated with side effects, particularly menstrual irregularity.26 Previous small trials suggest that the effectiveness of spironolactone may be similar to oral tetracycline for acne, but comparable data are limited.26 Ongoing trials of spironolactone vs oral tetracycline for acne mean that more information should be available in the next few years.27 28

Baseline check of renal function and potassium levels is advised prior to commencing spironolactone for acne.17 However, large observational studies show that abnormal renal function or potassium levels are very unusual in this population.29 Ongoing monitoring is unnecessary for most young women,17 and has recently been advocated just for women aged over 45 years.29 Spironolactone is less teratogenic than oral tetracyclines commonly used for acne,30 so it would be appropriate for spironolactone to be treated with no special restriction beyond contraceptive counselling, as is the case for oral tetracyclines.

Spironolactone is not currently licensed for the treatment of acne. However,NHS England advises that clinicians can use a licenced medicine outside its licenced indication (off-label prescribing) if they are satisfied that there is sufficient safety and efficacy evidence.31

## Isotretinoin

The oral retinoid isotretinoin is used for treating severe acne. It was originally marketed under the brand name Roaccutane®. It is required to be prescribed under a specialist with expertise in the use of systemic retinoids. The Medicines and Healthcare products Regulatory Agency (MHRA) licensed indication for isotretinoin is for severe forms of acne (such as nodular or conglobate acne, or acne that is at risk of permanent scarring) that is resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.23 32 Acne conglobate (severe nodular cystic acne) and acne fulminans (acne conglobate with systemic symptoms) require urgent specialist dermatology review and potentially earliery treatment with isotretinoin. . Otherwise, it is first necessary to follow the stepwise management of acne recommended in the NICE guidance.

Isotretinoin is an effective treatment for severe acne.14 There are a number of known and potential adverse effects associated with treatment.33 Most people will experience dryness of the skin and lips, which can be helped by emollients and lip balm, and a flare in acne is common at the start of treatment.33 Both of these side effects are dose dependent. Blood abnormalities are reasonably common, but in healthy people are usually not serious.34

Isotretinoin is highly teratogenic and therefore pregnancy must be avoided during treatment and for 1 month after stopping. All people with child-bearing potential (people who may be able to become pregnant) must be entered into the Pregnancy Prevention Programme (PPP).

Psychiatric and sexual dysfunction adverse effects are the focus of a new Expert Working Group of the Commission on Human Medicines report and have led to new MHRA guidance.32 The effect of isotretinoin on mood remains controversial; new population based studies have not shown an increased risk of suicide,35 however there are reports of individual distressing cases. The MHRA have recommended better provision of information to patients regarding possible risk of mental health and sexual function adverse effects; standardised assessment of mental health prior to starting and improved monitoring for adverse effects whilst on treatment.32 Patients under the age of 18 years require two health professionals to agree their acne is severe and that isotretinoin is the most appropriate treatment before initiation of isotretinoin therapy. The aim of these changes is to improve the safety of isotretinoin for the treatment of acne..

New compulsory risk minimisation materials have been developed including an Acknowledgement of Risk form for all patients (which includes the PPP for appropriate patients), a Patient Reminder Card and a Pharmacist checklist. These materials are produced and circulated by the Market Authorisation holders. Patient information and other supporting and training resources are freely available on the British Association of Dermatologists Isotretinoin Clinical Resources webpage (<https://www.bad.org.uk/guidelines-and-standards/isotretinoin-clinical-resources/>).

In the future, new studies are needed to further investigate these potential adverse effects, including the effect of a reduced isotretinoin dose on effectiveness and reduction of potential harms.36

# Management of acne in skin of colour

# The NICE guidance does not provide different treatment recommendations for acne in skin of colour. Post-inflammatory hyperpigmentation and scarring are more frequent and a particular concern for people with skin of colour and acne, and both atrophic and keloid scarring have been reported to be more common.37 It is important to avoid significant irritation with acne treatments, as this can worsen hyperpigmentation, but topical retinoids and azelaic acid can help both acne and hyperpigmentation.38

# Management of acne in primary care

**Urgent referral** (same day) is required for acne fulminans (acne conglobata associated with systemic symptoms)

**Specialist referral** is recommended by NICE for

* Nodulocystic acne or acne conglobata (severe nodulo-cystic acne with interconnecting sinuses and abscesses)
* Diagnostic uncertainty
* Mild to moderate acne that has not responded to two completed courses of treatment (see table 2)
* Moderate to severe acne which has not responded to treatment that includes an oral antibiotic
* acne scarring or persistent pigmentary changes
* acne contributing to persistent psychological distress or mental health disorder
* acne linked to medication use, including self-administered anabolic steroids

**Pharmacy management**

NHS England describes mild acne as a condition appropriate for self-management with pharmacy advice and use of over-the-counter medicine.39 Effective topical treatment (benzoyl peroxide) is available via pharmacies and many already offer advice about acne.40

# Conclusion

Early effective treatment for acne improves patient well-being and may prevent permanent scars or pigment changes. Initial management includes a range of topical treatments, with the option of adding oral antibiotics for patients with more severe acne. There are significant opportunities for reducing oral antibiotic prescribing in acne. These include: promoting effective use of topical treatments; avoiding prolonged courses of oral antibiotics; co-prescribing topical treatments alongside oral antibiotics; continuing topical treatments as maintenance treatment and considering alternatives, such as the COCP and spironolactone in primary care. When acne is unresponsive to these measures, timely referral for consideration of isotretinoin should be initiated.

# References

1. 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. *Journal of Investigative Dermatology* 2014;134(6):1527-34.

2. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *The Lancet* 2012;379(9813):361-72. doi: 10.1016/s0140-6736(11)60321-8

3. Bhate K, Williams H. Epidemiology of acne vulgaris. *British Journal of Dermatology* 2013;168(3):474-85.

4. Hassan J, Grogan S, Clark-Carter D, et al. The individual health burden of acne: appearance-related distress in male and female adolescents and adults with back, chest and facial acne. *Journal of health psychology* 2009;14(8):1105-18.

5. Lown M, McKeown S, Stuart B, et al. Prescribing of long-term antibiotics to adolescents in primary care: a retrospective cohort study. Br J Gen Pract. 2021;71:e887-e894.

6. National Institute for Health and Care Excellence. Clinical Knowledge Summaries acne vulgaris [online], 2023. Available: https://cks.nice.org.uk/topics/acne-vulgaris/ [Accessed 26 October 2023].

7. Ip A, Muller I, Geraghty A, et al. Young people's perceptions of acne and acne treatments: secondary analysis of qualitative interview data. *British Journal of Dermatology* 2020;183(2):349-56.

8. Ip A, Muller I, Geraghty AW, et al. Views and experiences of people with acne vulgaris and healthcare professionals about treatments: systematic review and thematic synthesis of qualitative research. *BMJ open* 2021;11(2):e041794.

9. Teede HJ, Tay CT, Laven J, et al. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. *Fertil Steril* 2023 doi: 10.1016/j.fertnstert.2023.07.025 [published Online First: 2023/08/17]

10. DermnetNZ. Acne due to a medicine [online], 2014. Available: https://dermnetnz.org/topics/acne-due-to-medicine [Accessed 26 October 2023].

11. Griffiths CEM, Barker J, Bleiker T, et al. Rook's Textbook of Dermatology. 9th edition. Chichester: Wiley Blackwell, 2016.

12. Corcoran L, Muller I, Layton AM, et al. Systematic review of clinical practice guidelines for acne vulgaris published between January 2017 and July 2021. *Skin Health and Disease* 2023;3(4):e240. doi: <https://doi.org/10.1002/ski2.240>

13. Ghodsi Z, Orawa H, Zouboulis CC. Prevalence, Severity, and Severity Risk Factors of Acne in High School Pupils: A Community-Based Study. *Journal of Investigative Dermatology* 2009;129(9):2136-41. doi: <https://doi.org/10.1038/jid.2009.47>

14. National Institute for Health and Care Excellence. Acne vulgaris: management (NG198) [online], 2021. Available: https://www.nice.org.uk/guidance/NG198 [Accessed 26 October 2023].

15. Mavranezouli I, Daly CH, Welton NJ, et al. A systematic review and network meta‐analysis of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris. *British Journal of Dermatology* 2022;187(5):639-49.

16. Xu J, Mavranezouli I, Kuznetsov L, et al. Management of acne vulgaris: summary of NICE guidance. BMJ 2021;374:n1800.

17. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol* 2016;74(5):945-73 e33. doi: 10.1016/j.jaad.2015.12.037

18. 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. *Journal of the American Academy of Dermatology* 2018;78(2):S1-S23. e1.

19. Platt D, Muller I, Sufraz A, et al. GPs’ perspectives on acne management in primary care: a qualitative interview study. *British Journal of General Practice* 2021;71(702):e78-e84.

20. Walsh TR, Efthimiou J, Dréno B. Systematic review of antibiotic resistance in acne: an increasing topical and oral threat. *The Lancet Infectious Diseases* 2016;16(3):e23-e33. doi: <http://dx.doi.org/10.1016/S1473-3099(15)00527-7>

21. Koo EB, Petersen TD, Kimball AB. Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris. *J Am Acad Dermatol* 2014;71(3):450-9. doi: 10.1016/j.jaad.2014.03.051

22. Arowojolu AO, Gallo MF, Lopez LM, et al. Combined oral contraceptive pills for treatment of acne (Review). *The Cochrane Library* 2012(7)

23. Joint Formulary Committee. British National Formulary [online]. 2023. Available: https://bnf.nice.org.uk/ [Accessed 26 October 2023].

24. Santer M, Lawrence M, Renz S, et al. Effectiveness of spironolactone for women with acne vulgaris (SAFA) in England and Wales: pragmatic, multicentre, phase 3, double blind, randomised controlled trial. *Bmj* 2023;381:e074349. doi: 10.1136/bmj-2022-074349

25. Santer M, Layton A. What do we know about prescribing spironolactone for acne? *Bmj* 2023;381:p1114. doi: 10.1136/bmj.p1114

26. Layton AM, Eady EA, Whitehouse H, et al. Oral Spironolactone for Acne Vulgaris in Adult Females: A Hybrid Systematic Review. *American journal of clinical dermatology* 2017;18(2):169-91. doi: 10.1007/s40257-016-0245-x [published Online First: 2017/02/06]

27. Poinas A, Lemoigne M, Le Naour S, et al. FASCE, the benefit of spironolactone for treating acne in women: study protocol for a randomized double-blind trial. *Trials* 2020;21(1):1-16.

28. Barbieri Lab. Spironolactone versus doxycycline for acne: a comparative non-inferiority evaluation (SD-ACNE) research study [online], 2023. Available: https://barbierilab.bwh.harvard.edu/clinical-trial-opportunities/ [Accessed 26 October 2023].

29. Thiede RM, Rastogi S, Nardone B, et al. Hyperkalemia in women with acne exposed to oral spironolactone: A retrospective study from the RADAR (Research on Adverse Drug Events and Reports) program. *International Journal of Women's Dermatology* 2019;5(3):155-57. doi: <https://doi.org/10.1016/j.ijwd.2019.04.024>

30. Liszewski W, Boull C. Lack of evidence for feminization of males exposed to spironolactone in utero: A systematic review. *Journal of the American Academy of Dermatology* 2019;80(4):1147-48.

31. Medicines & Healthcare products Regulatory Agency [Available from: <https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities> accessed 23 May 2023.

32. Medicines & Healthcare products Regulatory Agency. Isotretinoin for severe acne: uses and effects [20 September 2023]. Available from: <https://www.gov.uk/government/publications/isotretinoin-for-severe-acne-uses-and-effects>.

33. Vallerand IA, Lewinson RT, Farris MS, et al. Efficacy and adverse events of oral isotretinoin for acne: a systematic review. *The British journal of dermatology* 2018;178(1):76-85. doi: 10.1111/bjd.15668 [published Online First: 2017/05/26]

34. Affleck A, Jackson D, Williams HC, et al. Is routine laboratory testing in healthy young patients taking isotretinoin necessary: a critically appraised topic. *The British journal of dermatology* 2022;187(6):857-65. doi: 10.1111/bjd.21840 [published Online First: 2022/08/21]

35. Paljarvi T, McPherson T, Luciano S, et al. Isotretinoin and adverse neuropsychiatric outcomes: retrospective cohort study using routine data\*. *British Journal of Dermatology* 2022;187(1):64-72. doi: <https://doi.org/10.1111/bjd.21049>

36. Daly AU, Baptista Gonçalves R, Lau E, et al. A systematic review of isotretinoin dosing in acne vulgaris. *JEADV Clinical Practice* 2023;2(3):432-49. doi: <https://doi.org/10.1002/jvc2.154>

37. Maruthappu T, Taylor M. Acne and rosacea in skin of colour. *Clinical and experimental dermatology* 2022;47(2):259-63. doi: 10.1111/ced.14994 [published Online First: 2021/10/29]

38. Chiang C, Ward M, Gooderham M. Dermatology: how to manage acne in skin of colour. *Drugs Context* 2022;11 doi: 10.7573/dic.2021-10-9 [published Online First: 2022/06/21]

39. NHSEngland. Guidance on conditions for which over the counter items should not routinely be prescribed in primary care 2018 [Available from: <https://www.england.nhs.uk/medicines-2/conditions-for-which-over-the-counter-items-should-not-routinely-be-prescribed/> accessed 16 November 2020.

40. Sonnex K, Thornley T, Fleming N, et al. Perceived current and future roles of UK-based community pharmacy professionals in the long-term management of acne. *Exploratory Research in Clinical and Social Pharmacy* 2023;11:100310. doi: <https://doi.org/10.1016/j.rcsop.2023.100310>