

Guidelines for the management of acne: recommendations from a French multidisciplinary group

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Conflicts of interest

None declared.

Developer: French Society of Dermatology

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Prior version: 2007

Target population: Patients with acne, excluding newborns, acne secondary to hormonal diseases or induced acne. Management of acne scars are not within the scope of these guidelines.

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Context of guideline development

These are the updated French best practice guidelines initially released in 2007.¹ In addition to the need to reappraise potential new evidence published since 2007, the following reasons motivated our revisiting of acne management:

- 1 Antibiotics: In particular, the World Health Organization claims the need to restrict antibiotic use to situations in which they are absolutely essential, in order to minimize the risk of emergence of bacterial resistance to antibiotics.² Furthermore, after having analysed the risk/benefit ratio of minocycline, French health authorities withdrew its indication for acne treatment in 2012.³
- 2 Isotretinoin: Controversies concerning the potentially increased risk of depression and inflammatory bowel diseases have emerged.
- 3 Hormonal therapy: In May 2013 the French Medicines Agency (ANSM) suspended the marketing authorization in France of medicinal products containing cyproterone

acetate/ethinylestradiol (2 mg/0.035 mg). It then asked the European Medicines Agency Pharmacovigilance Risk-Assessment Committee (EMA PRAC) to reassess concerns regarding hormone-therapy-associated thromboembolism to decide whether the marketing authorization for it should be maintained, varied, suspended or withdrawn. PRAC concluded that the benefits of cyproterone acetate/ethinylestradiol (2 mg/0.035 mg) outweigh the risks and recommended the implementation of measures to minimize the risk of thromboembolism. Following this report ANSM withdrew the suspension.⁴

Guideline development

Methodology and participants

The 'Clinical Practice Guidelines' method established by the French National Authority for Health (Haute Autorité de Santé, HAS) was followed.⁵ The Working Group (WG) comprised 19 people: dermatologists (7); drug-safety specialist (1); endocrinologist (1); infectious diseases specialist (1); microbiologist (1); psychiatrist (1); paediatrician (1); gynaecologists (2); general practitioners (2); and HAS methodologists (2). In accordance with HAS policy,⁶ WG members and technical review authors had no conflicts of interest (COIs). COI declarations were examined by the HAS Ethics and Independent Expertise Committee COI.⁷

Literature search to technical review to guidelines procedure

An HAS health librarian conducted a literature search (see Supplementary Information Material S1 for sources and equations) for references from 2007 to September 2014 on the following topics: acne grading systems, influencing factors, interventions to improve adherence, efficacy and safety of topical and systemic treatments, bacterial resistance to antibiotics, physical therapies. Six physicians with skills in methodology (Master's degree or PhD) extracted data from each report, entered them into an extraction table, analysed methodology and risk of bias using Appraisal of Guidelines for REsearch & Evaluation (AGREE)⁸ for guidelines, Assessing Methodological quality for SysTematic Reviews (AMSTAR)⁹ for systematic reviews and the Risk-of-Bias tool for randomized controlled trials (Cochrane collaboration).¹⁰ Based on these analyses, they drafted the technical review that served as the basis for the WG's meetings and discussions to devise guidelines and recommendations. The ensuing initial version of the guideline served as the basis for all future work. It and the technical report were submitted to four acne experts, who were then interviewed for their opinions. Thereafter, the WG revised, if necessary, the first version of the guideline and recommendations. These documents were then submitted online (via the HAS website) to a peer review group of 51 physicians from different specialties, representing those in the WG, who gave

a formal opinion on the content and form of the initial version of the guideline, in particular its applicability, acceptability and readability. Each guideline recommendation was rated on a Likert scale from 1 (totally disagree) to 9 (fully agree) for form and substance. Recommendations that achieved a < 90% mean score > 5 had to be reexamined by the WG. Recommendation grades are described in Table 1 and guideline rating according to AGREE in Table 2.

Process for updating these guidelines

The literature search conducted on 28 July 2016 (sources and equations in Supplementary Material SM1) identified 63 new references since the last search (September 2014). After selection, 34 were included for analysis in the update, which is ongoing. The technical report will be revised with new evidence and resubmitted to the WG. Should the WG deem that a modification of the current guidelines would be useful, an updating process will be launched.

Table 1 Recommendation grades according to the French National Authority for Health for clinical practice guidelines⁵

Level of evidence (from the literature)	Grade
Level 1	A
Powerful randomized comparative trials	Established scientific evidence
Meta-analysis of randomized comparative trials	
Decision analysis based on well-conducted studies	
Level 2	B
Less powerful randomized comparative trials	Scientific presumption
Well-conducted nonrandomized comparative studies	
Cohort studies	C
Level 3	
Case-control studies	Low level of evidence
Level 4	C
Comparative studies with considerable bias	Low level of evidence
Retrospective studies	
Case series	Consensual Working Group opinion (CWGO)
If no data are available, recommendations are based on consensus among Working Group members after consulting the External Review Group. Absence of gradation does not mean that these recommendations are not adequate or useless. However, they must encourage further studies	

Table 2 Guideline-rating according to the AGREE tool^a

Domain	% of maximum possible score	Reasons for low rating
1 Scope and purpose	67%	
2 Stakeholder involvement	67%	One patient initially accepted the invitation to participate in the Working Group; however, she was not present at any meeting. There were three patients in the peer review group; however, we considered it was not enough to properly rate our guidelines for this item
3 Rigour of development	77%	
4 Clarity of presentation	77%	
5 Applicability	25%	The guideline did not describe facilitators and barriers to its application. The potential resource implications of applying the recommendations have not been considered. The guideline did not present monitoring and/or auditing criteria
6 Editorial independence	92%	

The Appraisal of Guidelines for REsearch & Evaluation (AGREE) instrument is a framework to: '(1) assess the quality of guidelines; (2) provide a methodological strategy for guideline development; and (3) inform what information and how it should be reported in guidelines'. AGREE II consists of 23 key items organized within six domains (each containing 3–8 items) followed by two global rating items ('Overall assessment'). Each item is graded on a Likert scale from 1 (strongly disagree) to 7 (strongly agree). Scores are calculated by all the individual item scores in a given domain and by scaling the total as a percentage of the maximum possible score for that domain'.

Evidence base

Among the 652 references identified by the literature search (79 guidelines, 53 systematic reviews, 232 randomized controlled trials (RCTs), 161 isotretinoin adverse effects, 47 epidemiology, 40 treatment adherence and 40 antibiotic resistance), 128 were included after selection. Among the numerous tools used to grade acne severity, none satisfied the mandatory essential clinical components.¹¹ Because the Global Acne Severity scale has been validated through an adequate process and provides a clear description of each grade supported by clinical photography, the WG chose to build its recommendations and base its algorithm on it.¹²

Recommendations according to acne severity are reported in the form of an algorithm (see Fig. 1). The WG considered poor treatment adherence to be a major concern (Table 3).

Specific recommendations for systemic treatments

Antibiotics

In light of the low level of evidence of antibiotic efficacies and the risk of inducing bacterial resistance to those drugs, the indication of topical antibiotics has been limited (Fig. 1). They must always be combined with a topical agent (benzoyl peroxide, retinoid or azelaic acid). Oral lymecycline or doxycycline prescriptions should always be limited to 3 months and combined with topical treatment. In light of the low level of evidence of oral erythromycin efficacy [no trial vs. placebo, four randomized controlled superiority trials vs. active comparator (doxycycline, $n = 1$, tetracycline, $n = 3$), of which none found a statistically significant

difference between groups]¹³ and the high level of resistance of some bacterial species to it, use of this antibiotic must be limited to cases with profoundly affected quality of life, contraindication to cyclines and failure of well-administered topical treatment.

Other systemic antibiotics have no indication to treat acne.

Hormonal therapy

When birth control is not required, combined oestrogen–progestin oral contraceptives are not indicated to treat acne. If a contraceptive method is needed, the prescription of combined oestrogen–progestin contraception should be assessed in terms of the risk/benefit ratio, notably the relative risk of thromboembolic events according to type of associated progestin.¹⁴ A combined oestrogen–progestin contraceptive containing levonorgestrel is recommended as first-line therapy, with norgestimate as the second-line choice. If acne persists despite dermatological treatments (topical treatments or systemic antibiotics), other hormonal treatments, including cyproterone acetate/ethinylestradiol (2 mg/0.035 mg), should be considered as an alternative.

Patients must be given information regarding the risk of thromboembolic events and thromboembolism risk factors must be sought before starting treatment.

Isotretinoin

Isotretinoin is recommended as second-line treatment for moderate to severe acne and as first-line treatment for very severe acne (Fig. 1). Regarding the risk of this treatment, a high level of evidence and concordant data support that isotretinoin does not increase the risk of inflammatory bowel disease. No available population-level data support that

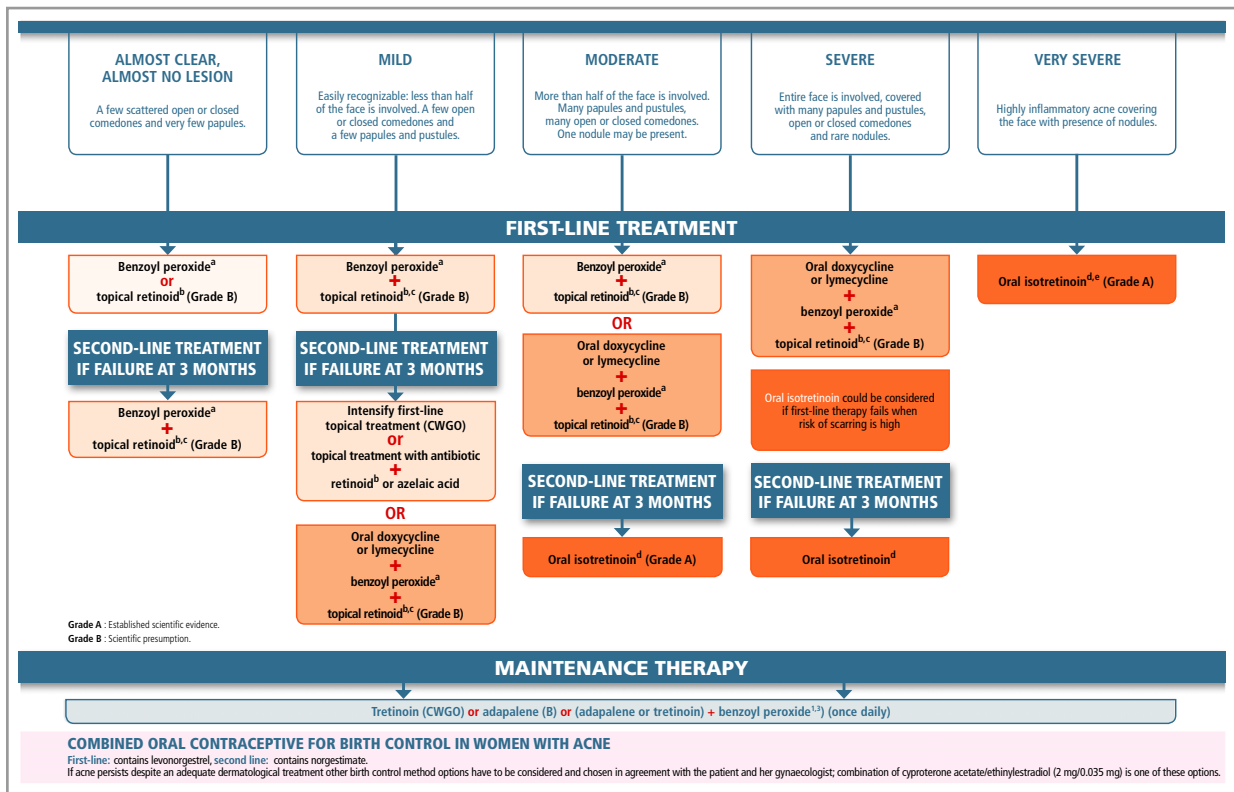


Fig 1. French guidelines for acne management: treatment algorithm for acne in adults and adolescents. For definitions of grades and Consensual Working Group opinion (CWGO), see Table 1. ^aNo trial has demonstrated the superiority of one benzoyl peroxide concentration over the others; no specific concentration is recommended. Patients must be informed of the risk of this product bleaching clothes. ^bConsidering the low level of evidence of comparative efficacies between different topical retinoid molecules and doses, no recommendation was given for a specific molecule or its dose. ^cIn the absence of a trial comparing the efficacies of and tolerances to the fixed-concentration adapalene 0.1%–benzoyl peroxide 2.5% vs. application of each molecule separately, and demonstration of better adherence, the fixed combination is not considered preferable. ^dOral isotretinoin is prescribed at 0.5 mg kg⁻¹ day⁻¹. Concerning isotretinoin-related adverse events, notably its teratogenicity, recommendations for its prescription must be strictly followed. ^eFor forms with numerous and severe comedones, oral isotretinoin should be started at a lower dose (0.2–0.3 mg kg⁻¹ day⁻¹) to lower the risk of an acne flare (CWGO). Reproduced (and translated into English) with permission from Le Cleach L, Lebrun-Vignes B, Bachelot A *et al.*; Société Française de Dermatologie. *Ann Dermatol Venerol* 2015; **142**(11):692–700. Copyright © 2015 Elsevier Masson SAS. All rights reserved.

Table 3 Patient counselling to enhance adherence

<p>To improve adherence (CWGO), inform the patient that:</p> <ul style="list-style-type: none"> Treatment (except isotretinoin) is not curative Treatment efficacy is not immediate; regular application and/or intake over several weeks is needed to obtain lesion improvement Maintenance therapy is mandatory once remission has been obtained by the induction regimen Local irritation frequently induced by topical treatments can be prevented by starting with application on alternating days and using moisturizers No dietary restrictions are recommended to attenuate acne (Grade C) <p>To improve adherence, patient preferences should be taken in consideration (CWGO). Should treatment fail, compliance has to be evaluated and more frequent consultations can be considered (Grade C) CWGO, consensual working group opinion; grades are defined in Table 1.</p>
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isotretinoin increases the risk of depression in, or suicide attempts by, patients suffering from acne; however, considering population and individual data, a rare individual risk could not be excluded. Before starting isotretinoin, the patient and his/her family circle must be informed of the potential risk of psychiatric disorders and the patient's treating physician must be notified of any mood or behaviour change. The Adolescent Depression Rating Scale can be used to help physicians detect mood changes in adolescents.¹⁵ Informing the patient's primary-care physician of isotretinoin prescription and the potential risk of psychiatric disorders is recommended. General good practice recommendations for isotretinoin prescription, notably prevention of pregnancy, are mandatory.¹⁶

The WG consensus concluded that evidence was too weak to support sequential (1 week or 10 consecutive days per month) or low-dose isotretinoin [$< 0.5 \text{ mg kg}^{-1}$ (0.25–0.4 mg kg⁻¹)].

Comparison with other current guidelines

American Academy of Dermatology

Release date February 2016; same scope (except included complementary/alternative therapy); last search September 2014.¹⁷

Differences from French Guidelines:

- Different grading system: mild, moderate and severe.
- Topical dapsone (not available in France) is one of the options for second-line treatment for mild acne.
- No restriction on the use of topical antibiotics.
- Minocycline is one oral antibiotic treatment option.
- Azithromycin is an option indicated in those who cannot use tetracyclines (i.e. pregnant women or children < 8 years of age).
- Trimethoprim–sulfamethoxazole and trimethoprim are considered for patients unable to tolerate tetracyclines or those who are treatment-resistant.
- Oral spironolactone is a second-line option for females with moderate or severe acne.
- Low-dose isotretinoin (0.2–0.4 mg kg⁻¹ daily) can be used to effectively treat acne and reduce the frequency and severity of medication-related side-effects.

European Dermatology Forum

Release date June 2016; same scope; last search July 2015.¹⁸

Differences from French Guidelines:

- Different grading system: Comedonal acne; Mild–moderate papulopustular acne; Severe papulopustular acne, moderate nodular acne; Severe nodular acne, conglobate acne.
- General recommendations not described as first-line and second-line therapy but as high strength of recommendation, medium strength of recommendation and low strength of recommendation.
- Fixed-association adapalene or clindamycin and benzoyl peroxide are recommended for mild to moderate papulopustular acne (high strength of recommendation).
- Minocycline is one of the systemic antibiotic options; however, doxycycline and lymecycline are preferred to minocycline and tetracycline.
- In severe papulopustular, moderate nodular acne and severe nodular, conglobate acne a low dose of systemic isotretinoin (maximum 0.3 mg kg⁻¹ daily) is one option for maintenance treatment (low strength of recommendation).

Evidence supporting the Working Group's decision on the discrepancies listed above

- Topical dapsone: we found no trial showing superiority or noninferiority over other topical treatments (treatment not marketed in France).

- Minocycline: based on one Cochrane review that found no evidence of a superiority of minocycline over other cyclines in acne treatment and expressed concerns on safety, and a pharmacovigilance survey highlighting the higher risk of serious adverse events with minocycline compared with doxycycline, minocycline has an unfavourable benefit/risk balance and was not recommended.^{3,19}
- Azithromycin: we found eight RCTs comparing azithromycin to tetracycline, doxycycline or minocycline in patients with acne including one unpublished RCT (NCT 00392223). One noninferiority trial including 240 patients found that azithromycin was not inferior to doxycycline.²⁰ Five RCTs not designed as noninferiority trials were not able to demonstrate any superiority of azithromycin vs. cyclines, and one found a superiority of doxycycline vs. azithromycin.²¹ The WG considered that these conflicting results and only one trial demonstrating noninferiority was of too low level of evidence to recommend azithromycin in acne treatment.
- Trimethoprim–sulfamethoxazole: this drug was not assessed in our technical review.
- Low-dose isotretinoin (0.25–0.4 mg kg⁻¹ daily): we found one RCT comparing high doses (oral isotretinoin 1 mg kg⁻¹ per day or every other day) to a low dose (20 mg every other day) during a 16-week trial. This trial was at high risk of bias due notably to the absence of blinding and absence of primary outcome.²² One trial compared isotretinoin 5 mg with placebo in low-grade adult acne.²³ One negative RCT was not able to find a difference between isotretinoin 0.5–0.7 mg kg⁻¹ daily and 0.25–0.4 mg kg⁻¹ daily for the primary outcome (Global acne grading system score and number of lesions).²⁴ Other studies were not comparative or not randomized. The WG considered there was a too low level of evidence to recommend low-dose isotretinoin.
- Oral spironolactone: acne secondary to hormonal diseases was not within the scope of these guidelines. One Cochrane review did not find any evidence of efficacy of spironolactone in acne treatment.²⁵ We did not find further RCTs published since the time of the search of the Cochrane review.
- Fixed-association adapalene and benzoyl peroxide: we did not find a RCT comparing efficacies of and tolerances with the fixed-concentration adapalene 0.1%–benzoyl peroxide 2.5% vs. application of adapalene 0.1% and benzoyl peroxide 2.5% separately rather than as a fixed combination (e.g. adapalene in the morning and benzoyl peroxide in the evening), or demonstrating better adherence to the fixed combination.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Material S1. Supporting information including: (i) Sources searched by the French National Health Authority (Haute Autorité de Santé) medical librarian; (ii) Search strategies in Medline and Embase databases; (iii) Criteria for study selection; and (iv) References included in French Guideline on acne management.