Appendix 3 (as supplied by the authors): Methods of the Canadian Acne Clinical Practice Guideline

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Appendix to: Asai Y, Baibergenova A, Dutil M, et al. Management of acne: Canadian clinical practice guideline. *CMAJ* 2015. DOI:10.1503/cmaj.140665.

Contents

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The Canadian Acne Clinical Practice Guidelines (CPG) were developed in accordance with criteria of the Appraisal of Guidelines Research and Evaluation-II (AGREE II) instrument[1] as well as the ADAPTE framework for guideline adaptation.[2]

This CPG was developed using a systematic process whereby: (1) existing CPGs were identified and reviewed, (2) one existing CPG was selected for adaptation based on high methodological quality, (3) systematic literature searches and evaluations were conducted to update treatment evidence and to include treatments available in Canada, and (4) online Delphi surveys were conducted to obtain consensus on treatment recommendations.

I. Nomination of Expert Panel

Canadian clinical experts in acne were nominated by two dermatologists on the steering community [JT and CL] based on the following criteria: national prominence in acne management, research in acne, or peer-reviewed publications in acne. An additional consideration for selection was inclusion of dermatologists from disparate regions in Canada for breadth of representation. Two clinicians with dual expertise in epidemiology and dermatology were invited to serve on the panel as methodological experts and were responsible for literature evaluation and grading of evidence. Inclusion of these epidemiologists was a means to reduce potential bias within the expert panel who were otherwise comprised of content experts.[3]

II. Literature Search, Review and Adaptation

II.1 Review of Existing Clinical Practice Guidelines

A systematic search of acne CPGs developed via a systematic, evidence-based process, and published from 2007 to 2013 revealed five such documents. Evaluation with AGREE II criteria[1] demonstrated two with particularly high methodological quality: *European Evidence-based (S3) Guidelines for the Treatment of Acne* (ES3)[4] and the Malaysian *Management of Acne*.[5] The ES3's strengths for adaptation included detailed description of search methodology, which would facilitate replication, and explicit disclosure of the process leading to specific recommendations.[6] In view of these methodological details, the ES3 guideline was selected as the basis for the adaptation of the Canadian Acne CPG.

II.2 Adaptation of Scope

The ES3 guidelines covered systemic, topical, and laser/light treatments available in Europe. For the purposes of the Canadian Acne CPG, the literature included in ES3 was updated to

March 2013 and expanded to include treatments available in Canada not covered in ES3; namely, fixed-dose combination clindamycin with tretinoin, topical dapsone, topical tazarotene, oral isotretinoin (Lidose formulation), chemical peels, diet and dairy, and adjunctive therapy including cleansers and skin care products.

II.3 Adaptation and Update of the ES3 Guidelines

The adaptation process included:

Updating the literature The ES3 guidelines were developed from a systematic evaluation of the literature from 1 January 1999 to 10 March 2010 for topical and systemic treatments and from 1 January 2007 to 13 April 2010 for laser and light treatments. In this adaptation, the evidence contained within ES3 was updated via a systematic search of the MEDLINE and EmBASE databases using the same criteria as ES3. The updated search encompassed the dates from 10 March 2010 to 1 March 2013 for topical, systemic, and adjunctive therapies and from 13 April 2010 to 1 March 2013 laser and light therapies. Search terms and strategies used to update the literature search are detailed in appendix 1.

An updated search performed on July 14, 2015 did not find any new research that required revisiting the Delphi process.

Literature search for expanded scope An additional systematic search for acne medications available in Canada but not covered by ES3 (topical tazarotene, dapsone, clindamycin/tretinoin combination; oral isotretinoin-Lidose) was conducted and encompassed the dates 1 January 1999 to 30 March 2013. Systematic searches for chemical peels and the effect of diet on acne were conducted for studies published between 10 March 2010 and 1 March 2013. Search terms and strategies used to extend the search beyond the scope of ES3 are detailed in appendix 1.

Literature selection Articles were selected based on the following criteria: English language, human/clinical studies dealing with the management of active acne, systematic reviews, meta-analyses, randomized controlled trials (RCTs), controlled prospective studies and new research-based primary publications. Furthermore, articles selected during primary search were restricted to those with original data, provided efficacy outcomes, had more than 10 patients per study arm, and represented treatments available in Canada.

Excluded were studies on chloracne, acne venenata, acne fulminans, acne necroticans, acne agminata, acne inversa (hidradenitis suppurativa), occupational acne and acne rosacea; as well as those using surrogate outcome measures only (for example, sebum production,

Propionibacterium acnes colony counts, patient ratings only). Eligibility for critical evaluation was based on the consensus opinion of two independent reviewers (AB and YA). Articles were independently reviewed by each reviewer and any discrepancies were resolved after discussion between the two reviewers.

Evaluation of trials Trial evaluation was similar to ES3 whereby the following grades were assigned to clinical studies:

- A Randomized, double-blind clinical trial of high quality (for example, sample-size calculation, flow chart of patient inclusion, intention-to-treat (ITT) analysis, sufficient sample size)
- B Randomized clinical trial of lesser quality (for example, only single-blind, limited sample size: at least 15 patients per study arm)
- C Comparative trial with severe methodological limitations (for example, not blinded, very small sample size, no randomization)

Evaluation of evidence for treatment efficacy Treatments were rated based on criteria established for each level of evidence, as shown below:

Level of Evidence 1 (LE 1)	Further research unlikely to change confidence in estimate of effect: At least two grade A trials available and results largely consistent with those of additional grade B or C studies
Level of Evidence 2 (LE 2)	Further research likely to have an important impact on confidence of estimate of effect and may change the estimate: At least three grade B trials and results largely consistent with any additional grade C trials
Level of Evidence 3 (LE 3)	Further research is very likely to have an important impact on confidence in estimate of effect and is likely to change the estimate: Conflicting evidence or limited number of trials, mostly grade B or C
Level of Evidence 4 (LE 4)	Any estimate of effect is very uncertain: Little or no systematic experimental evidence; trials are extremely limited in number and/or quality

III. Operationalization of the Working Group

Treatments were categorized into one of (1) topicals, (2) systemics, (3) devices, or (4) adjunctive and were allocated between nine expert panel members for critical review and

authorship. At least two panel members were assigned to each topic with each member involved in no more than two sections.

III.1 Formulation of Recommendations

Recommendations were based on consensus of the expert panel (excluding CL and JT) during blinded voting conducted by an online Delphi process. Recommendations for each treatment within the categories of acne were proposed by the two critical literature evaluators (AK and YA). Recommendations were either directly transposed from ES3, were modified from ES3 based on new evidence, or were novel recommendations for treatments not covered by ES3. Rationale for each recommendation was given, including evidence of efficacy and safety, and the level of evidence available. Cost information was provided but no specific methodology was outlined to the expert panel for integration of this information into recommendations.

Each panelist then anonymously voted one of three ways: to accept, to increase, or to decrease the strength of recommendation. They also had an opportunity to provide a comment on their vote. These results were recorded by an independent facilitator. In cases where consensus was not reached, anonymized aggregate feedback, including comments stating rationale in support of different recommendations, was to be provided to the panelists for their consideration prior to a subsequent round of voting.

Three online Delphi surveys were performed to obtain consensus, defined as 2/3 majority of the nine panelists. In the first Delphi survey, the categories of recommendation were scrutinized. Consensus was achieved to remove the category ‘May not be used under any circumstances’. In the second and third, voting to accept or change the treatment recommendations proposed by the literature evaluators was undertaken. Consensus for all recommendations was obtained with a single round.

III.2 Nature of Recommendations

Recommendations were voted upon by the expert panel for each treatment and for each of the following categories of acne:

1. Comedonal Acne
2. Mild-to-Moderate Papulopustular Acne
3. Severe Acne

These categories differ from those of ES3 in that the two severe categories from ES3 (severe papulopustular and moderate nodular; and severe nodular and conglobate) are condensed into a singular severe category. This condensation was undertaken from recommendations by the

expert panel based on clinical relevance and overall efficiency due to overlap of treatments of the two severe categories in ES3.

For each of these, an online Delphi survey of the expert panel obtained a consensus recommendation of one of the following strengths:

- High strength — strongly recommended
- Medium strength — can be recommended
- Low strength — can be considered
- Negative — not recommended
- Open — a recommendation for or against cannot be made currently

III.3 Presentation of Evidence

For each treatment considered for recommendation, the mechanism of action, evidence for efficacy, and known risks and adverse events are discussed in the guidelines. The level of evidence (LE) and trial grades described in section II.1 are given to facilitate interpretation of efficacy data. Information regarding safety of medications during pregnancy are given, when available, using the Pregnancy Categories (A, B, C, D, and X) designated by the United States Food and Drug Association (FDA). While the latter may be evolving to a narrative description of fetal risk, the categorical system was used due to maintain consistency with prior reporting. We anticipate the use of narrative summaries with more universal reporting in the future.

IV. Consultation, Endorsement, and Testing

Prior to publication of the Canadian Acne CPG, input was sought from the stakeholders. The draft manuscript was reviewed and comments solicited from the following groups and institutions: a discussion group of university students (University of Windsor, Windsor, Ontario, Canada), Canadian Dermatology Association, Canadian Skin Patient Alliance, Canadian Dermatology Nurses Association, Canadian Pharmacists Association, the Canadian Family Physician Association, and authors of the ES3 guidelines.

A listing of comments and feedback from these groups was compiled and shortcomings considered important and consistently identified were addressed in the manuscript.

Pilot testing of the CPG was conducted in an author's dermatology clinic during April and May, 2014.

V. Applicability

Factors related to applicability of these guidelines, including facilitators and barriers to application, advice on putting recommendations into practice, resource implications, and criteria for monitoring and auditing, are discussed in Section IV of the full length CPG (Appendix 3).

VI. Updating

This document will be updated for validity every five years. Updates may be provided sooner than scheduled, as required, to include significant new developments such as evidence on existing benefits and harms of interventions, development of new treatments, or changes in available treatments.

VII. Editorial Independence and Conflict Declaration

VII.1 Mitigation of External Influence

These guidelines were developed independently by the authors and the contents and treatment recommendations represent their collective opinion based on best evidence. The following steps were implemented to ensure the recommendations were free from external influence by industry, third party payers or governmental agencies.

1. Exclusion of the panel members involved in solicitation of funding (JT, CL) from writing and voting on treatment sections
2. Non-disclosure of funding pharmaceutical company identities until the final draft of the manuscript was submission-ready
3. Exclusion of funding pharmaceutical company input into the conception, design, and development of the CPG project or in the writing of the final manuscript
4. Invitation of all pharmaceutical and cosmetic companies offering acne products to participate as funding sponsors for unrestricted educational grants

Funds obtained were used for travel, accommodation, and meal expenses of the expert panel and the administrative support group. Honoraria for expert panel participation were declined by unanimous voting by the panel, thus none were remunerated (including JT and CL).

VII.2 Conflict of Interest

Explicit and complete declaration of conflicts of interest regarding industry involvement (financial, professional, personal) was required of all panel members and is detailed here:

- Y. Asai served on an advisory board for GSK.
- A. Baibergenova has served on an advisory board for Galderma, Valeant, and Astellas.
- M. Dutil has received honoraria for speaking from Galderma, Valeant, GSK, and L'Oreal.
- P. Hull has no conflicts to declare.

- S. Humphrey has served as a speaker and consultant to Galderma, GSK, Johnson & Johnson, Procter & Gamble and Valeant and as an investigator for Galderma.
- C. Lynde has served as a clinical investigator, speaker or consultant to Cipher Pharma, Galderma, Johnson & Johnson, Stiefel, and Valeant.
- Y. Poulin has received research funding from Galderma, Dermira and Photocure ASA.
- N. Shear has acted as a consultant to Valeant, and Galderma.
- J.Tan has been an advisor to Cipher, Galderma, Stiefel/GSK, Merz, Photocure, Valeant; consultant to Galderma, Merz, Roche; clinical investigator for Allergan, Cipher, Dermira, Galderma, Stiefel/GSK, and Photocure.
- J. Toole has served as a consultant and speaker for Valeant, Stiefel, Roche, and Galderma.
- C. Zip has participated on advisory boards for Valeant, and Galderma.

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