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## Perspectives on Isotretinoin and the Canadian Consensus Guidelines on Treatment of Acne

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### ABSTRACT

*Treatment objectives and pharmacoeconomic considerations are important when developing guidelines that are effective and rational. Canadian Acne Treatment Guidelines were last published in 1995. New guidelines were recently developed to incorporate therapeutic advances and data from more recent studies. Isotretinoin fulfills the major objectives of acne treatment and has clear pharmacoeconomic advantages when compared to conventional rotational oral antibiotics, antiandrogens and topical therapy in the treatment of moderate-to-severe acne. It should be considered the standard of treatment for scarring acne and moderate-to-severe non-scarring acne.*

**KEY WORDS:** *Acne Vulgaris, Isotretinoin, guidelines*

The treatment of any condition must comprise the following objectives, either singly or in combination:

- cure
- prevention of recurrence
- limitation of structural or functional deterioration
- prevention of complications
- relief of signs and symptoms
- maintenance of comfort and dignity
- preservation of self-esteem.<sup>1</sup>

These objectives as well as pharmacoeconomic considerations are of particular importance in the development of clinical guidelines that are effective and rational. Since the publication of the last Canadian Acne Treatment Guidelines in 1995, some of these issues have been further elucidated.<sup>2</sup> The new Canadian Consensus Guidelines for Treatment of Acne Vulgaris and Prevention of Acne Scarring<sup>3</sup> were developed to incorporate therapeutic advances and information from recent epidemiological, pharmacoeconomic, and psychometric studies of acne.

### Definition of Severe Acne

Severe acne in earlier guidelines<sup>2</sup> was defined as the combined presence of numerous comedones, papules, nodules and multiple scars. In contrast, the new Canadian Consensus Guidelines are based on the Consensus Panel of Acne Classification<sup>20</sup> definition of severe acne, in which the diagnosis is based on the presence of any of the following:

- persistent or recurrent inflammatory nodules
- extensive papulopustular disease
- ongoing scarring
- persistent purulent and/or serosanguineous drainage from lesions
- presence of sinus tracts
- psychosocial and occupational impact
- inadequate therapeutic response.

The presence of acne scars and the severity of inflammatory lesions are independent indicators of severe acne. The current guidelines were developed to emphasize the need for appropriate clinical sensitivity to the presence of scarring.

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## Relief of Signs and Symptoms

The efficacy of isotretinoin in reducing inflammatory acne lesions is presently unrivalled. In a comparative study of isotretinoin (1mg/kg/day) and minocycline (100mg daily for 4 months) the reduction in mean acne grade was approximately 90% and 50%, respectively.<sup>4</sup> While no studies directly compare hormonal therapy to isotretinoin, *Diane-50* (ethinyl estradiol 50ug and cyproterone acetate 2mg) was shown to be equal but not superior in efficacy to tetracycline 500mg bid after 6 months of therapy.<sup>5</sup> *Diane-35* (ethinyl estradiol 35ug and cyproterone acetate 2mg) has been demonstrated to result in a clinically significant reduction in lesion counts and acne grade after six treatment cycles. Rates and duration of remission were not assessed.<sup>6</sup> *Ortho Tricyclen* (ethinyl estradiol 35ug and a triphasic regimen of norgestimate) has been shown to reduce total acne lesion counts by 47-53% after six cycles of therapy. However, the length of remission on discontinuation of therapy was not assessed in these studies.<sup>7,8</sup>

## Cure or Long-term Remission

The sole therapy with demonstrable ability to achieve cure or long-term remission is isotretinoin, given at a standard dose of 1mg/kg. In 179 patients treated with a single course of isotretinoin and follow-up at 3 years, White, et al<sup>9</sup>, found a long-term remission rate of 39% in those treated with a minimum cumulative dose of 100mg/kg. Recurrences requiring only topical therapy were observed in 17%. Twenty-five percent required oral antibiotics, while 19% required further courses of isotretinoin.<sup>9</sup> In a 10-year study of 88 patients by Layton, et al<sup>10</sup>, 40% required no further therapy while 21% required only topical therapy. Sixteen percent required oral antibiotics while 23% required further courses of isotretinoin.<sup>10</sup> In these studies, total cumulative doses exceeding 100mg/kg and 120mg/kg, respectively, produced significantly better results than lower dose regimens.

In contrast, oral antibiotics are not considered to be curative, nor are they remitting agents in the treatment of acne. The 5-year relapse rate for patients taking oral antibiotics has been estimated at 83%.<sup>11,12</sup> In a 6-month study of 62 patients, those treated with *Diane-50* alone or in combination with tetracycline 500mg bid continued to maintain improvement in acne grade and lesional counts 2 months after completion of treatment, whereas these parameters deteriorated in those treated with tetracycline alone.<sup>5</sup> Minocycline, 100mg daily for 4 months, has been shown to reduce the mean acne grade by roughly 50%. However, 6 months after treatment, acne grades had deteriorated and approached pre-treatment scores. This tendency to relapse has also been demonstrated with tetracycline. In contrast, isotretinoin resulted in a significantly greater degree of mean acne grade improvement that persisted 6 months after completion of therapy.<sup>4</sup> The rates and durability of remission for patients treated with hormonal agents has not been quantified.

## Limiting Structural Deterioration

The primary structural sequela of active acne is scarring. Layton, et al<sup>13</sup>, found that scarring affected 95% of 185 acne patients attending their clinic. They also observed that superficial inflammatory papules, not just nodular acne, might be associated with the development of scars. Furthermore, their data showed that inadequately treated acne of up to 3 years duration correlated significantly with an increased risk of scarring. In the only study assessing the effect of early medical intervention on subsequent scarring caused by acne, Layton, et al<sup>4</sup>, observed that the mean scarring score in patients given isotretinoin after 3 years acne duration was significantly higher than in those who had received isotretinoin less than 3 years after acne onset. This suggests that less scarring develops in those receiving isotretinoin early in their disease process.<sup>4</sup>

Parameter	Isotretinoin	Oral antibiotics	Hormones
Efficacy	+++	++	++
Cure or long term remission	++	-	?
Prevention of scars	++	?	?
Self-esteem	++	+	?

Table 1: Comparison of isotretinoin with other treatment regimes for acne vulgaris.

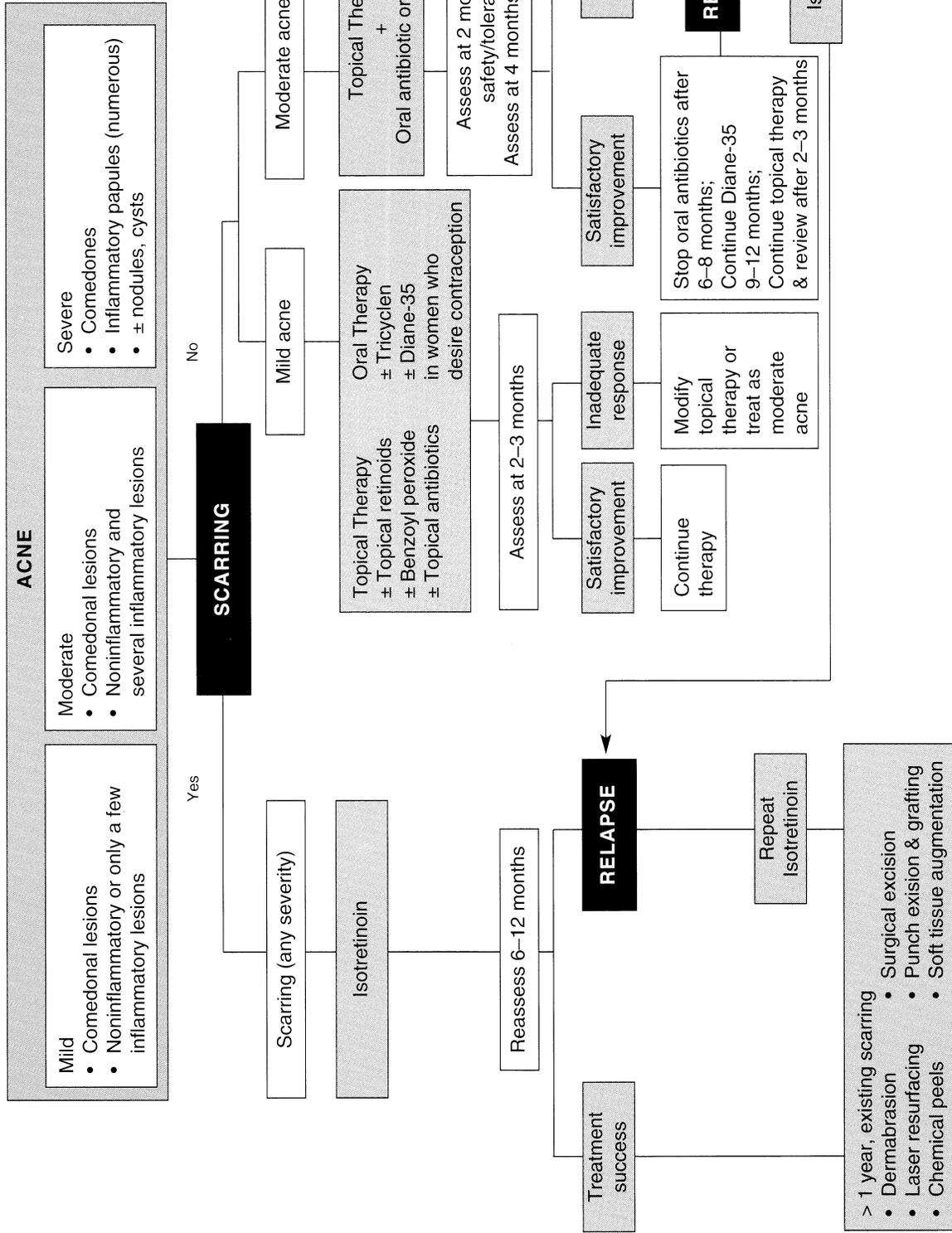


Figure 1: Flow chart for acne management. Reprinted with permission from Maddin WS, Landells IDR, Poulin Y, et al. Treatment of acne vulgaris and prevention of acne scarring. *J Cutan Med Surg* 4(supp. 1):S4-1 to S4-13 (2000).

## Psychometric Assessments

To properly assess scarring, all areas should be examined. This includes the back, shoulders, neck and chest, and the face. The effect of the scars and the active disease on the patient's psychological status should also be assessed when determining the severity of the disease. If the scarring and/or psychosocial impact is significant, the grade and treatment of acne should be escalated accordingly. Figure 1 (page 3) depicts an algorithm to assist clinicians in determining their options.<sup>3</sup>

## Maintaining Comfort and Dignity or Preserving Self-esteem

Psychometric assessments have demonstrated that treatment with isotretinoin results in significant improvement in the psychological impact of acne.<sup>4,14</sup> Furthermore, while improvement in clinical acne grade, and psychosocial disability can be seen in those treated with isotretinoin and minocycline after 4 months, the improvement in both parameters was significantly greater for isotretinoin.<sup>4</sup>

## Pharmacoeconomic Analysis

Pharmacoeconomic analyses of isotretinoin have demonstrated cost-benefit, cost-effectiveness, and cost-minimization advantages compared to conventional rotational oral antibiotics, antiandrogens and topical therapy in treatment of moderate-to-severe acne.<sup>11,12,14,15</sup> A recent cost-minimization analysis compared costs of treatment with the following:

- (1) isotretinoin on diagnosis with re-treatment based on reported rates of relapse
- (2) rotational oral antibiotics
- (3) rotational oral antibiotics with females of child-bearing age also receiving *Diane*
- (4) rotational oral antibiotics with isotretinoin only after failure of two antibiotics used for 3 months each.

This study demonstrated that the time for cost equivalence to the isotretinoin regimen was 50 months for rotational oral antibiotics, 35 months for oral antibiotics and *Diane*, and 10 months for the group receiving isotretinoin after two courses of failed oral antibiotics.<sup>15,16</sup> The latter regimen is similar to that recommended by the previous Canadian Guidelines for Treatment of Acne, in which up to 3 courses of rotational antibiotics each lasting 4–6 months, was advised prior to consideration of isotretinoin.<sup>2</sup> Those recommendations would have resulted in even more costly treatment. Furthermore, delaying effective therapy for 12–18 months would likely increase the risk and costs associated with treatment of acne scarring and psychosocial disturbances.

## Adverse Effects

Although these systemic agents may be associated with adverse effects, the majority of these are mild, well tolerated, and manageable by dosage adjustment or symptomatic therapy. Serious adverse events are rare and include teratogenicity and

possibly depression with isotretinoin<sup>17</sup>, thromboembolic events with hormonal contraceptives<sup>18</sup>, and hypersensitivity reactions with oral antibiotics.<sup>19</sup>

The new Canadian Consensus Guidelines differ from the earlier, 1995 version by:

- emphasizing acne scarring as the primary decision point for initial therapy
- recommending early treatment with isotretinoin if acne scars are present
- advancing treatment to isotretinoin after failure of a single course of systemic antibiotics or hormonal therapy at 4 months.

The use of this drug fulfills the major objectives of acne treatment and has clear pharmacoeconomic advantages. Accordingly, it should be considered the standard of treatment for scarring acne and moderate-to-severe non-scarring acne.

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# US FDA Advisory Committee Meetings Held to Discuss Isotretinoin, Safety Issues and a New Accutane Formulation

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There is no drug that has provided as much therapeutic benefit for 12 million acne patients as this retinoid has done in the past 18 years following its introduction. However, it is a retinoid and, therefore, a teratogen. In spite of the elaborate pregnancy prevention program put in place by Hoffman-LaRoche, as well as a tracking program monitored by the Slone Epidemiology Unit in Boston Massachusetts, there are patients taking isotretinoin who still get pregnant. More recently, adverse psychiatric events have surfaced in patients who have taken isotretinoin (*Accutane*).

Such adverse events triggered these meetings called by the US FDA. On September 18th and 19th a joint meeting of the Dermatologic and Ophthalmic Drug/Pharmaceutical Science Advisory Committees met to discuss three issues with regard to isotretinoin (*Accutane*):

- risk management regarding pregnancy and isotretinoin use
- possible link with psychiatric events
- a new formulation (*Accutane NF*) for which an NDA was submitted by Hoffman-LaRoche in October 1999.

## Day 1

On the first day of meetings, risk management options to prevent pregnancy in patients taking *Accutane* were explored by the Committee. Discussions included Roche's revised US Pregnancy Prevention Program (Targeted PPP or T-PPP). The Committee recommended that a risk management program for pregnancy prevention should consist of Roche's T-PPP, a mandatory physician and patient enrollment, as well as establishing a linkage between the pharmacy that dispenses an *Accutane* prescription and confirmation of negative pregnancy test results for the patient.

## Day 2

The second day of meetings focused on risk management options for psychiatric events and *Accutane NF*, Roche's new formulation.

In light of the lack of clear linkage between depressive illness and *Accutane*, an opinion expressed by several FDA Committee members, the Committee defeated a motion to expand the registry to include all patients, and to include questions about psychiatric illness in the registry's informed consent database. Currently, the registry only includes women in their childbearing years. But, the committee did recommend that Roche and NIH fund additional research in this area including a basic science study on retinoids and retinoid receptors in the adolescent and adult brain, prospective controlled studies, etc.

The Committee supported the new formulation because the dosage is less than the current formulation, and there is a reduced variability of drug absorption when taken with or without food. However, they noted that there could be possible consequences associated with the simultaneous availability of the two formulations for both patients and prescribers. Roche stated that it will be launching *Accutane NF* in very different packaging than the original formulation and will be providing additional information on the new formulation to prescribers.

## Conclusion

By the end of the meetings, the Dermatologic and Ophthalmic Drug/Pharmaceutical Science Advisory Committees supported the new formulation (*Accutane NF*). The Committee agreed that there was at present no causal link between psychiatric events and *Accutane*. In spite of this, they recommended additional research with regard to possible psychiatric connections to *Accutane*, as well as the establishment of a registry to track women who are in their childbearing years taking *Accutane*. Challenges await Hoffman-LaRoche and the US FDA in establishing such a registry. It will be interesting to follow their progress.

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## Update on Drugs

Class	Name/Company	Approval Dates and Comments
<b>Transdermal Agents</b>	<b>Estradiol Transdermal System</b> <i>Vivelle</i> Novoagyne Pharmaceuticals	The US FDA approved the additional indication of postmenopausal osteoporosis in August 2000, for this transdermal estrogen patch. <i>Vivelle</i> has been available for the treatment of menopausal symptoms since March 1996.
<b>Antibacterial Agents</b>	<b>Levofloxacin Tablets/Injection</b> <i>Levaquin Tablets/Injection</i> Ortho Pharmaceuticals	The US FDA approved an additional indication of treating complicated skin and skin structure infections at a higher dose of 750mg once daily in September 2000. This is the ninth indication for Levaquin, which has been marketed in 250mg and 500mg doses since 1993.
<b>Photo-aging</b>	<b>Tretinoin Cream</b> <i>Renova 0.02%</i> Ortho Pharmaceuticals	The US FDA approved this new formulation in August 2000, for reducing fine facial wrinkles associated with chronic sun exposure and the natural aging process. This new <i>Renova</i> formulation must be used as part of a total skin care and sun protection program. It is expected to be available by prescription in November 2000.
<b>Photo-aging</b>	<b>Tretinoin Cream</b> <i>Renova 0.05%</i> Ortho Pharmaceuticals	The US FDA approved a new indication in September 2000, as an adjunctive agent for use in the mitigation of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin in patients who use comprehensive skin care and sunlight avoidance programs.
<b>Vaginal Preparations</b>	<b>Butoconazole Nitrate</b> <i>Gynazole 2% vaginal cream</i> KV Pharmaceuticals	The US FDA approved this vaginal cream in June 2000, for the treatment of vaginal yeast infections with only one dose. It is available by prescription in prefilled applicators for use during the day or night.
<b>Antiviral Agent</b>	<b>Docosanol 10% Cream</b> Avanir Pharmaceuticals	The US FDA approved this antiviral agent in July 2000, for the treatment of recurrent oral-facial herpes simplex infections. It is the first FDA approved cold sore treatment to be available OTC.
<b>Atopic Dermatitis Agents</b>	<b>Tacrolimus Ointment</b> <i>Protopic</i> Fujisawa Healthcare	An NDA was submitted to the US FDA in July 2000, for this ointment for short and long-term treatment of the signs and symptoms of atopic dermatitis in adults and in children 24 months and older.
<b>Drug News</b>		
<b>Antirejection Agents</b>	Sangstat Medical Corporation voluntarily recalled the generic form of cyclosporine ( <i>SangCya</i> ) in July 2000, because it was found not to be bioequivalent to <i>Neoral</i> oral solution when mixed with apple juice as recommended in its labelling. The US FDA approved this generic formulation in May 1999.	
<b>AIDS Related Kaposi's Sarcoma</b>	Officials from the Centers for Disease Control and Prevention in Atlanta, Georgia, say that the incidence of AIDS related Kaposi's sarcoma (KS) continues to decline in the US, thanks in large part to the widespread use of effective combination antiretroviral therapies. Between 1990 and 1998, the incidence of KS declined approximately 8.8%.	

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