The information contained in this Consensus Conference on the Safe and Optimal Use of Isotretinoin is provided for educational purpose only. The American Academy of Dermatology invited a panel of recognized experts to participate in the Consensus Conference, which was held in February 2002. The information contained herein has been carefully reviewed and represents the consensus opinions of those experts at the time this report was prepared. It is not intended to establish exclusive course(s) of treatment and is not intended to establish practice parameters, mandatory guidelines, or standards of care.

American Academy of Dermatology Consensus Conference* on the Safe and Optimal Use of Isotretinoin: Summary and recommendations

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INTRODUCTION

Isotretinoin (13-cis-retinoic acid) received United States Food and Drug Administration (FDA) approval for treatment of severe recalcitrant nodular acne in 1982.[1] Today, it is used to treat a spectrum of dermatologic conditions. The efficacy of isotretinoin in treating severe nodular acne, disorders of cornification, and chemoprevention of non-melanoma cutaneous carcinoma in high-risk individuals is well documented.[2] For some patients unresponsive to other standard therapies , isotretinoin is a miracle drug.

Of growing concern are the serious adverse side effects, including teratogenesis; elevations in triglyceride, and to a lesser degree cholesterol levels; liver enzyme elevations; potential skeletal abnormalities

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during long-term use; and most recently, an association with depression or suicide. As such, new proposals for regulating the use of isotretinoin have arisen.

Within the American Academy of Dermatology (AAD), there is concern that proposals for regulating the use of isotretinoin may not be supported by scientific data, and this led to an AAD consensus conference that brought together more than 40 experts. Consensus conference participants, who included experts in teratology, epidemiology, gynecology, psychiatry, basic scientists, a representative form the FDA, and a broad representation of dermatologists convened to hear expert testimony, review scientific data, and produce a consensus document about isotretinoin that promotes the highest standards, in dermatologic prectice and serves as a resouce for governmental bodies and regulatory agencies.

CONFERENCE GOALS

Three goals provided a discussion framework for the conference participants:

- To bring scientific clarity to unresolved questions regarding isotretinoin use.
- To present the best data on the clinical use of isotretinoin, data related to pregnancy and isotretinoin use, and data on adolescent psychiatry and isotretinoin use.
- To develop recommendations regarding future research efforts related to these areas.

CONFERENCE PROCEEDINGS

The conference commenced with a welcome from the 2001 AAD President Ronald G. Wheeland, MD (Santa Fe, New Mexico), and introductions form Dr Wheeland and Conference Chair Lowell A. Goldsmith, MD (Rochester, New York), who stated, "We have to assume that isotretinoin will remain in our armamentarium, and to address the issues that have not been adequately addressed in other settings."

Following the introductions, expert testimony was presented in four areas: (1) clinical use of isotretinoin, (2) pregnancy and isotretinoin ,(3)adolescent psychiatry and isotretinoin, and (4) FDA prespective. During the first presentation, "Clinical Use of Isotretinoin" (moderated by Dr Wheeland), Donald P. Lookingbill, MD (Jacksonville, Florida), gave participants an overview of isotretinoin and acknowledged that the quality of life is greatly improved in patients with a variety of acne types and severities. Dr Lookingbill also addressed concerns and shared techniques used in his own practice. When prescribing isotretinoin, he advises starting isotretinoin at 0.5 mg/kg/day for the first four weeks of treatment to avoid flares before increasing to the full dosage of 1.0

mg/kg. Dr Lookingbill also stated the need to be vigilant about depressive symptoms.

A panel presentation, "Pregnancy and Isotretinoin" (moderated by Jean L. Bolognia, MD, of New Haven, Connecticut), followed. This presentation covered the risk of teratogenesis, an epidemiologic study of pregnancy prevention for women on isotretinoin (Accutane), and contraception failures and practice. James L. Mills, MD, MS, a teratologist with the National Institute of Health (Bethesda, Maryland) emphasized, "There is no safe level of exposure during embryogenesis. All therapeutic doses are potent enough for malformations, including cranio-facial defects, cardiac defects, and retardation". According to Mills, the rate of malformation with retinoid exposure is about 20 percent, compared to 2 percent in the unexposed population.

"Depression, Suicide and Isotretinoin" (moderated by Suephy C. Chen, MD, from Atlanta, Georgia) looked at available studies on the topic. Dr Chen explained that "the few available studies on the topic are methodologically flawed." Eric Caine, MD, a psychiatrist from the University of Rochester (Rochester, New York), acknowledged this lack of causation and advised dermatologist to be cognizant of risk factors for suicide and quickly seek consultative assistance when questions or concerns arise. He also exhorted dermatologists to develop standards for reporting depression and suicide in their practices.

Jonathan K. Wilkin, MD, Director of Dermatologic and Dental Drug Products at the FDA, wrapped up the presentation by introducing the FDA's perspective, stating that there is no doubt about the teratogenesis of isotretinoin; however, more scientific data about the possible psychological side effects are needed. In his speech, Dr Wilkin also praised the AAD's efforts to examine this critical issue and develop a consensus statement that will guide the safe use of this agent.

Following Dr Wilkin's presentation, conference paticipants, who were previously assigned to three breakout groups for the purpose of addressing designated focus questions and capturing their ideas, met. Each group was asked to specifically address questions related to 3 topics: (1) clinical uses of isotretinoin, (2) reproductive concerns and isotretinoin use, and (3)depression, suicide, and isotretinoin. The next day, participants gathered to hear each group's spokesperson report the findings.

Subsequent to the consensus conference, members of the planning committee developed a draft consensus statement based on the conference results. The AAD Board of Directors reviewed the draft consensus statement at its meeting in May 2002 and determined that it would seek member input

on the draft consensus statement before approving the document. This request for member input, along with the draft consensus statement, was published in the June 2002 issue of Dermatology World. Below is the Board-approved AAD Final Consensus Statement on the safe and optimal use of isotretinoin.

FINAL AAD CONSENSUS STATEMENT ON THE SAFE AND OPTIMAL USE OF ISOTRETINOIN

Introduction

Oral retinoids, which are potent derivatives of vitamin A, have proven to be important life altering drugs that have improved the quality of life of hundreds of thousands of patients over the past two decades. The safe and prudent use of these important agents is essential because these drugs have the potential for unwanted effects on the individual and the fetus of pregnant women.

A consensus conference with a broad representation of dermatologists, other physicians, and basic scientists was convened by the AAD on February 20-21, 2002 to consider approaches for improving the safe administration of isotretinoin. A summary of the conference follows.

I-Clinical uses of isotretinoin

What is the clinical spectrum of dermatologic disease that responds to isotretinoin? How should patients taking isotretinoin be managed (aside from pregnancy and psychiatric issues)?

A.When should isotretinoin be used? There is sufficient evidence for the use of isotretinoin in severe forms of acne, particularly cystic acne or acne which has proven refractory to other forms of therapy. Assessment of severity includes the impact of the disease on the patient. The decision to prescribe isotretinoin should be based on a discussion between the informed patient and physician, taking into consideration the severity of the acne, the presence or the potential for scarring, risks, benefits, therapeutic alternatives, safety, and cost.

B. What data are available and how strong is the evidence for the use of isotretinoin for other dermatologic diseases? In addition to the treatment of acne, isotretinoin has been demonstrated to be effective in the treatment of disorders of cornification and chemoprevention of skin cancer in high risk individuals who are actively developing multiple basal cell and squamous cell carcinomas. Such patients include those with xeroderma pigmentosum, the nevoid basal cell carcinoma syndrome, or those who are immunosuppressed (eg, individuals receiving immunosuppressive agents to prevent organ transplant rejection).

There are individual case reports and case series suggesting efficacy in other dermatological conditions. It is recommended that data be collected prospectively, generating information about the safety and efficacy of isotretinoin for other diseases such as cutaneous lupus erythematosus, acne rosacea, and hidradenitis suppurativa; this information should then lead to double-blind, randomized, controlled trials to assess their effectiveness. The safety of isotretinoin when used chronically for such diseases should be prospectively investigated.

C.How should the patient receiving isotretinoin be monitored for toxic effects, including bone and lipid abnormalities? The most common laboratory abnormalities in patients taking isotretinoin are elevations in triglyceride and, to a lesser degree, in cholesterol levels. Therefore, periodic monitoring of serum triglycerides and cholesterol is recommended in individuals receiving isotretinoin. Although liver enzyme elevations are usually mild, reversible, and rarely clinically significant, monitoring of transaminases (alanine aminotransferase and aspartate aminotransferase) is recommended and should be based upon dosage and patient characteristics, including comorbid factors. There is no consensus on monitoring other laboratory parameters including complete blood counts, muscle- and pancreas-derived enzymes, or serum calcium levels.

The diseases being treated and the duration of treatment are important in determining the need to monitor for potential skeletal abnormalities. Monitoring skeletal toxicity during a single course of isotretinoin therapy is generally not indicated. Repeated short courses or long-term use of isotretinoin (beyond the usual 20-week course for acne) may require monitoring for skeletal toxicity.

II.Reproductive concerns and isotretinoin use

What are optimal guidelines for avoidance of the risk of pregnancy during isotretinoin use? How can compliance among physicians and patients be maximized?

A. Is there a therapeutic dose of oral isotretinoin that does not have adverse effects on the fetus? There is no dose of oral isotretinoin that is safe for use during pregnancy.

B. Are there practice patterns for physicians that can be improved to reduce the risk of pregnancy during isotretinoin exposure? Every woman who has reached menarche is at risk for becoming pregnant unless she has had a hysterectomy or is definitely post-menopausal. In the general US population, approximately half of all pregnancies are unplanned. All women between puberty and menopause are at risk, including those who have indicated that they

have not been or are not sexually active when isotretinoin is begun, because they may become sexually active during therapy.

Therefore, all physicians and other providers who prescribe isotretinoin must ensure that contraceptive counseling is provided to all women and insist that patients use two contraceptive methods as outlined in the isotretinoin package insert. Dermatologists may wish to refer their patients to a gynecologist or to the patient's primary care provider for contraceptive counseling and administration of contraceptives. (Complete sexual abstinence, when adhered to, is an effective means of contraception.) Avoidance of pregnancy is ultimately the responsibility of the male and female engaged in sexual intercourse. Regardless of a physician's counseling, treatment, and oversight, pregnancy can occur if men and women abrogate their responsibility.

Ten percent of women in the Slone survey[4] who reported pregnancies were pregnant at the time that isotretinoin was first administered.

Strict adherence to the pregnancy testing guidelines in the isotretinoin packaging insert is necessary. Particularly important is a second pregnancy test. Performed at the onset of menses; that is required before starting isotretinoin because bleeding at the time of implantation may simulate a menstrual period and human chorionic gonadotropin levels may not increase until 7 to 9 days after fertilization.

For the woman who has had intercourse without the use of two forms of effective contraception as detailed in the package insert, emergency contraception is an option. The details of emergency contraception are outlined in Table I.

A thorough history of concomitant medications and dietary/herbal supplements is important because these may interfere with contaceptive effectiveness.

C.What groups of women are at highest risk for pregnancy during isotretinoin use? Based on the Slone data for women who enrolled between 1989 and 1999, women between the ages of 25 and 35 years had the highest pregnancy rate (3.7 pregnancies per 1000 courses of isotretinoin). This compares with a rate of 2.8 pregnancies per 1000 isotretinoin courses in women between the ages of 15 to 24 years. Pregnancies occurred in all age groups, but the rate were lower among women under 15 and over 34. The pregnancy rates per 1000 courses of isotretinoin for age < 15 years, 35 to 44 years, and ≥ 45 years were 1.0, 1.7 , and 0.5 , respectively. Dermatologists prescribe approximately 85% of all isotretinoin. Among women who have isotretinoin exposed pregnancies, a similar proportion

(approximately 85%) received their isotretinoin prescriptions form dermatologists.

Patients should not be pregnant before the initiation of therapy and should not become pregnant during therapy and for one month after discontinuation of isotretinoin.

D.What issues associated with use of contraceptives are important to dermatologists? Effective contraception is essential in minimizing the risk of isotretinoin associated teratogenicity. The recommended use of two contraceptive methods maximizes protection as outlined in the product insert. Table I has detailed supplemental information on the effectiveness of individual forms of contraception. Some dermatologists may choose to refer their patients for contraception management.

Dermtologists would benefit from educational forums regarding reproductive endocrinology and the use and prescribing of contraceptive methods, including emergency contraception.

In summary, it is essential to:

- Increase dermatologists' voluntary compliance with the recommended pregnancy prevention guidelines for the use of isotretinoin.
- Increase patient participation in the Slone epidemiological study and similar studies and report collected data to dermatologists on an ongoing basis.
- Encourage AAD sponsorship of educational forums on reproductive endocrinology and contraception, including methods for emergency contraception, when receiving teratogenic drugs.
- Appoint a liaison committee with the American College of Obstetric and Gynecology to develop guidelines for contraception, including emergency contraception when using teratogenic drugs.

III.Depression, Suicide, and Isotretinoin

What are optimal guidelines for detection and management of depression before and during isotretinoin use?

Suicide and depression are major public health concerns, and their painful impact on individuals and their families cannot be over-emphasized. Depression and suicide are common in adolescents, but occur in other age groups as well. Suicide is the third most common cause of death in the 15 to 24 year age group, and second most common cause of death in the 25-34 year age group.

Recently, substantial concern regarding the relationship between isotretinoin and depression or suicide has emerged, both in the medical and public arenas. Epidemiological studies to date have not shown an association between isotretinoin and depression or suicide because acne itself may be a risk factor for depression. Some physicians have observed

Table I. Percentage of US women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception and the percentage continuing use at the end of the first year

method	% women experiencing an unintended pregnancy within the first year of use		% women continuing use at one year ‡
	typical use*	perfect use†	
No method §	85	85	--
Spermicides ‖	29	15	42
Withdrawal	27	4	43
Periodic abstinence	25	--	51
Calendar	--	9	--
Ovulation method	--	3	--
Sympto-thermal	--	2	--
Post-ovulation	--	1	--
Cap			
Parous women	32	26	46
Nulliparous women	16	9	57
Sponge			
Parous women	32	20	46
Nulliparous women	16	9	57
Diaphragm #	16	6	57
Condom**			
Female (Reality)	21	5	49
Male	15	2	53
Combined pill and minipill	8	0.3	68
Evra patch	8	0.3	68
NuvaRing	8	0.3	68
Depo-Provera	3	0.3	56
Lunelle	3	0.05	56
IUD			
Progestasert (progesterone T)	2.0	1.5	81
ParaGard (copper T)	0.8	0.6	78
Mirena (LNg IUS)	0.1	0.1	81
Norplant and Norplant-2	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.10	100

Emergency contraceptive pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.††

Lactational amenorrhea method: LAM is a highly effective, temporary method of contraception. ‡‡

Source : Trussell J. Contraceptive efficacy. In: Hatcher RA, Trussel J, Stewart F, et al. Contraceptive technology: Eighteenth revised edition. New York : Ardent Media; 2002.

*Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

†Among couples who initiate use of a method (not necesarily for the first time), and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

Amond couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

§ The percentages becoming pregnant in columns 2 and 3 are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (10 85%) to represent the percentage who would become pregnat within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

‖ Foams, creams, gels, vaginal suppositories, and vaginal film.

¶ Cervical mucus (ovulation)method supplemented by calendar in the pre-ovulatory and basal body temperature in the post ovulatory phases.

With spermicidal cream or jelly.

**Without spermicides.

††The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. Plan B (1 dose is 1 white pill) and Preven (1 dose is 2 blue pills) are the only dedicated products specifically marketed for emergency contraception. The FDA has in addition declared the following 13 brands of oral contraceptives to be safe and effective for emergency contraception: Ovral or Ogestrel (1 dose is 2 white pills), Alesse or Levlite (1 dose is 5 pink pills), Aviane (1 dose is 5 orange pills), Nordette or Levlen (1 dose is 4 light-orange pills), Lo/Ovral, Levora or Low Ogestrel (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills), and Trivora (1 dose is 4 pink pills).

‡‡However , to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

what they interpreted as a causal relationship with mood changes and depression in a limited number of patients. These uncontrolled clinical observations have not yet been examined in a rigorous and prospective manner. In addition, there is paucity of basic science literature on the effect of retinoids on adult brain function.

The primary concern of physicians must be for the safety of the patient. The AAD supports additional education for dermatologist in the evaluation of risk factors of depression and suicide in isotretinoin patients.

A.What are the risk factors for depression or suicide that can be recognized by the treating physician? There are known risk factors associated with depression or suicide in the general population. The risk factors for suicide include mood disorders, clinical depression, bipolar disease, personality disorders (especially conduct disorders), a feeling of hopelessness, substance abuse (especially alcohol), behavioral problems at home and school, violent behavior, recent experience of stressful life events, family history of psychiatric disorders, domestic violence, access to firearms, and other social turmoil.

Data has not been published on the outcome of patients undergoing mood or suicide screening before beginning therapy with isotretinoin. For individual patients, clinicians may elicit such information by inquiring about a potential isotretinoin candidate's social and developmental history including school problems, volatile home life, developmental problems, family history of mood disorders, other psychiatric disease, substance abuse, or suicide attempt.

Individuals with any of these risk factors should have close monitoring for mood disorders. Any patient in whom a significant risk of suicide is recognized needs emergency medical and mental health evaluation and care, and immediate discontinuation of isotretinoin.

B. Would a standardized, validated psychiatric instrument (eg,the Center for Epidemiologic Studies-Depression (CES-D) Scale, the Cardiff Scale, or the Beck Scale) be a useful tool for screening and monitoring symptoms of depression in patients receiving isotretinoin? If so, what is the preferred instrument? There are no data that mood or suicide screening is beneficial for patients begining isotretinoin therapy. Several instruments are available to quantify mood complaints or personal distress on an investigational basis, but the utility of these instruments has not been demonstrated outside of a research setting. The development and/or validation of treatment specific tools that would be suitable for use in dermatology practice settings to monitor these patients is supported by members of this

conference.

C. Are there absolute or relative psychiatric contraindications to isotretinoin therapy? There are no known absolute or relative psychiatric contraindications to isotretinoin therapy in a patient who is carefully monitored. Patients with a known history of prior suicide attempts should be referred to a mental health professional prior to the initation of acne therapy with isotretinoin.

D. What parameters would be included for analysis in a well-designed clinical investigation of a possible association between isotretinoin and depression/suicide? There are a variety of investigational approaches that may be useful in examining the possible association between isotretinoin and mood changes or suicide. Future studies would optimally draw upon multidisciplinary teams of dermatologists, adolescent medicine specialists, psychologists, psychiatrists, pharmacologists, epidemiologists, and other professionals.

A coordinated approach would include a complementary array of studies in three main categories: (1) basic (fundamental research aimed toward elucidating mechanisms of brain action); (2) population-oriented research (including appropriately-designed large scale epidemiologic studies; and (3) individual-oriented research, such as large prospective, controlled incidence studies of patients who have experienced retinoid-associated unwanted effects.

There also needs to be a major effort to expand and integrate basic science research starting at the molecular level and including the total spectrum, such as pharmacology, toxicology, genetics, pharmacogenomics with large-scale epidemiologic studies, and large, prospective controlled incidence studies.

Subsets of these studies may include: subjects with a new onset of mood changes, challenge/rechallenge, and further characterization of social, medical, and psychiatric parameters in case of suicide. These may be best examined as separate cohorts in a national cooperative effort.

E. If psychiatric side effects can be attributed to isotretinoin, are they dose-dependent? There are no published data addressing this issue.

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