

Oral Isotretinoin: An Analysis of Its Utilization in a Managed Care Organization

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ABSTRACT

OBJECTIVE: To assess utilization of oral isotretinoin within a managed care organization.

METHODS: A retrospective analysis of pharmacy and medical claims from a southern California HMO was performed to (1) determine the prescribing patterns of oral isotretinoin from 1997 to 2000, stratified by age and gender, (2) categorize and quantify the use of antiacne prescriptions in the 6-month period immediately prior to the first oral isotretinoin prescription claim observed during this study; and (3) identify the amount of oral isotretinoin dispensed in a 210-day period following the dispensing date of the first oral isotretinoin prescription.

RESULTS: The number of prescriptions was distributed almost equally between males and females, and the average number of prescriptions dispensed per patient decreased with age. A total of 39% of patients who received an oral isotretinoin prescription had not received a prescription for any antiacne medication in the preceding 6 months, and an additional 31% had not received a prescription for a topical retinoid. Approximately 27% of patients received more than a 150-day supply within the 210-day period following the first oral isotretinoin claim.

CONCLUSIONS: These data suggest that in the 6 months preceding the first observed oral isotretinoin prescription, up to 70% of patients had not received a trial of a topical retinoid before receiving oral isotretinoin even though the product labeling advises that oral isotretinoin should be used only in patients unresponsive to "conventional therapy" (which is generally defined as at least a topical retinoid plus an oral antibiotic). Up to 27% of patients appeared to continue a course of treatment for longer than the 15-20 weeks advised in the isotretinoin product labeling.

KEYWORDS: Isotretinoin, Retinoids, Prescribing patterns, Acne, Antiacne, Acne treatment guidelines, Managed care

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Retinoids are the mainstay of treatment for acne vulgaris because they act at the core of the pathophysiologic problem—excessive keratinization in the follicles of the skin.¹ By promoting normalization of this keratinization, retinoids help to ensure that sloughed epithelial cells and sebum drain from the follicles. As a result, they are helpful not only in clearing blocked follicles (both subclinical microcomedones and visible comedones) but also in preventing the development of new microcomedones. And, as microcomedones are the precursor of all other acne lesions, inhibiting their development prevents the formation of both noninflammatory and inflammatory acne lesions.

For optimum efficacy and tolerability, antiacne treatment usually consists of two or more medications with differing mechanisms of action. Thus, a topical retinoid (with its keratolytic effect) may be used in conjunction with an antibiotic and/or benzoyl peroxide (for their antibacterial action) to treat mild or moderate inflammatory lesions. Three topically applied retinoids—tazarotene, tretinoin, and adapalene—are used widely for the treatment of mild and moderate acne. For more severe inflammatory acne, or if greater antibacterial efficacy is required, a topical retinoid is more likely to be used in conjunction with an oral antibiotic. And, if this does not achieve sufficient efficacy, then the only oral retinoid currently indicated for the treatment of acne—oral isotretinoin—would be considered.

According to the product labeling information approved by the FDA, oral isotretinoin should be reserved for severe recalcitrant nodular acne and used only if the patient has been unresponsive to conventional therapy, including systemic antibiotics (Table 1). (Conventional therapy is not defined in the product labeling, but many dermatologists define conventional therapy as a trial of at least a topical retinoid and an oral antibiotic.) The American Academy of Dermatology guidelines for the treatment of acne vulgaris also recommend that oral isotretinoin be used primarily for severe, recalcitrant, cystic acne that is refractory to conventional antiacne measures, including systemic antibiotics.² For females of childbearing potential, they also recommend the use of oral isotretinoin only if severe disfiguring cystic acne is present. Recent Canadian consensus guidelines suggest a more aggressive approach in the management of acne vulgaris with the primary goal of preventing scarring.³ These guidelines suggest that any patients requiring treatment for acne who already have evidence of acne scarring should be offered oral isotretinoin, regardless of the severity of their disease.

TABLE 1 Product Labeling Information for Oral Isotretinoin⁴

Indications and Usage

Oral isotretinoin is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. "Severe," by definition, means "many" as opposed to "few or several" nodules. Because of significant adverse effects associated with its use, oral isotretinoin should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics.

A single course of therapy has been shown to result in complete and prolonged remission of disease in many patients. If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course because experience has shown that patients may continue to improve while off oral isotretinoin.

Dosage and Administration

The recommended dosage range for oral isotretinoin is 0.5 mg/kg to 2 mg/kg in 2 divided doses daily for 15 to 20 weeks.

The restrictions in the use of oral isotretinoin arise because it is associated with a high risk of birth defects during pregnancy,⁴ a high risk of mucocutaneous adverse effects,⁵ and, possibly, an enhanced risk of depression (which has been raised by some but refuted by others).⁶⁻⁹ Despite regulatory and patient education efforts by the U.S. Food and Drug Administration and the drug's manufacturer,¹⁰ the isotretinoin-exposed pregnancies occur at a higher rate than expected.¹¹ In an attempt to minimize the potential for isotretinoin-exposed pregnancies, several changes have been made to the FDA-approved labeling since July 1998 when the manufacturer-supported Pregnancy Prevention Program was

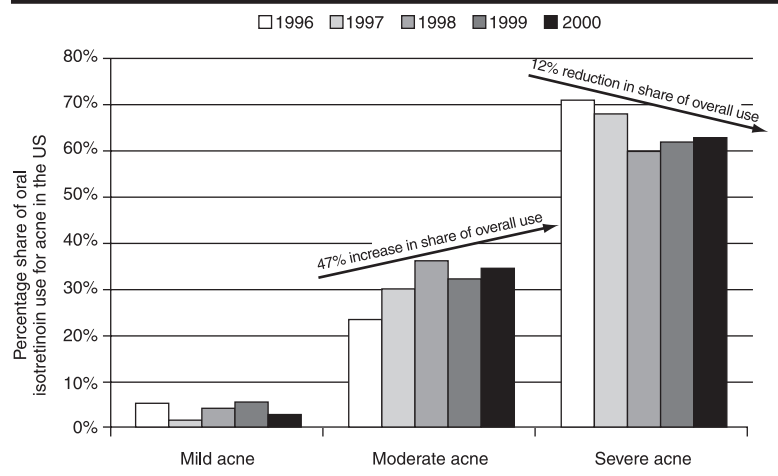
first started. These include ensuring, beginning in April 2000, that at least one of the two reliable means of contraception be used simultaneously as a primary method (tubal ligation, partner's vasectomy, birth control pills, injectable/implantable birth control products, or an intrauterine device). In addition, since January 2001, patients are required to read a medication guide for isotretinoin.

The latest change, in April 2002, introduced an enhanced risk management program, known as SMART—the System to Manage Accutane Related Teratogenicity. This program involves prescribers, pharmacists, and patients in measures to reduce the potential for isotretinoin-exposed pregnancy. Prescribers are required to read the *SMART Guide to Best Practices* and enroll in the SMART Program in order to receive the Accutane qualification stickers that are required for pharmacists to dispense any isotretinoin prescription. In addition, physicians are asked to ensure that they prescribe the drug to female patients of childbearing potential only if the patient has had two negative pregnancy tests before receiving the drug and continues to have additional negative pregnancy tests at monthly intervals throughout treatment. Also, female patients of childbearing potential are required to commit to using two reliable forms of contraception immediately before, during, and after therapy. As it does not appear possible to completely avoid patient-related contraceptive failures,¹² it is essential that physicians' prescribing of the drug is appropriate. In general, practitioners or specialists with substantial experience are trusted to prescribe appropriately even when the patterns do not appear to coincide with the guidelines.

Analysis of market research data between 1996 and 2000 shows that, during this period, the use of oral isotretinoin in acne increased by 144% in patients with moderate acne and by 46% in patients with severe acne.¹¹ As a result, there has been an increase in the proportion of oral isotretinoin use in acne accounted for by patients with moderate acne (from 23% to 35%), and a decrease in the proportion of such use in patients with severe acne (from 71% to 63%) (Figure 1).¹³

These national data suggest that approximately 37% of oral isotretinoin use in acne is in patients who do not have severe acne even though the product labeling advises that the drug be reserved for patients with severe recalcitrant nodular cystic acne. It is perhaps unexpected to observe the above-mentioned changes in prescribing patterns taking place despite the strong warnings about birth defects associated with oral isotretinoin and the introduction of other topical retinoids during the same time period (e.g., tazarotene, adapalene, and a microsphere formulation of tretinoin) offering better safety and similar efficacy in less severe cases of acne. As such a large proportion of prescriptions do not adhere to the labeling information, it is likely that some patients might be

FIGURE 1 The Percentage Share of Oral Isotretinoin Use for Acne in the U.S. by Severity



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TABLE 2 Number of Prescriptions for Acne Medications Among the 2.08 Million Members of a Managed Care Organization Over a One-Year Period¹

Age (Years)	Female						Male						Total
	< 10	10–19	20–34	35–54	55–64	> 65	< 10	10–19	20–34	35–54	55–64	> 65	
Oral Isotretinoin	6	4,965	4,950	2,400	60	24	24	7,743	2,334	987	132	102	23,727
Topical retinoid*	492	11,574	9,549	3,927	480	468	2,001	10,779	2,691	1,998	240	273	44,472
Topical antibiotic†‡	69	3,459	4,524	4,392	918	1,929	45	2,802	1,143	1,644	444	1,218	22,587
Topical BPO††	0	453	375	216	3	12	9	321	171	126	0	0	1,686
Topical BPO-antibiotic combination§	114	11,226	6,363	4,074	105	93	87	12,039	2,400	1,329	159	108	38,097
Azelaic acid	0	576	624	189	12	15	0	453	78	15	0	0	1,962

* Includes adapalene, tazarotene, tretinoin (generic and brands: Retin-A, Retin-Micro, Avita)

† Includes clindamycin (Cleocin T gel and lotion, Clinda-Derm lotion), erythromycin (Erycette, Eryderm, Erymax, Erygel, Akne-mycin)

†† Includes benzoyl peroxide (Brevoxyl, Benzac)

§ Includes BPO/erythromycin combination (Benzamycin)

¹Data from 4/1/00 to 8/31/00 (but extrapolated to full year) in overall general population without study exclusions

²Only those topical antibiotics most likely to be used for the treatment of acne are included (to exclude prescriptions given for other uses)

TABLE 3 Derivation of the Overall Acne Population

Year	Patients Who Had Been Diagnosed with Acne Vulgaris or Who Had Received a Prescription Acne Medication	Patients Excluded Due to Lack of Continuous Enrollment (% Acne Population)	Patients Excluded Due to Presence of Other Skin Diseases* (% Acne Population Continuously Enrolled)	Overall Acne Population (Excludes Patients with Lack of Continuous Enrollment and Presence of Other Skin Diseases)
1997	36,043	5,658 (15.7)	768 (2.5)	29,617 (82.2)
1998	51,804	6,636 (12.8)	1,382 (3.1)	43,786 (84.5)
1999	55,163	7,316 (13.3)	1,004 (2.1)	46,843 (84.9)
2000†	70,065	7,540 (10.8)	7,631 (12.2)	54,894 (78.4)
Average Per Year	53,269	6,788 (12.7)	2,696 (5.8)	43,783 (82.2)

*Mycosis fungoides/cutaneous T-cell lymphoma, rosacea, psoriasis, ichthyosis congenital, White's Disease, or "other dermatoses" (ICD-9 diagnosis code of 757.39)

† Year-2000 data extrapolated to full year (data was extracted from 1/1/97 to 8/31/00)

able to manage their acne using safer drugs.

To further investigate the utilization of oral isotretinoin, particularly with regard to the product labeling information, a retrospective analysis of pharmacy and medical claims was performed.

Methods

This was a retrospective database analysis of pharmacy and medical claims from a large mixed-model HMO located in 5 Western states. The study consisted of 2 parts. The objective of the first part was to investigate patterns of oral isotretinoin utilization during each calendar year from January 1997 through August 2000. The objective of the second part was to evaluate actual oral isotretinoin

utilization with regard to the product labeling information. This included examining the pattern of utilization of other antiacne medications in the 6-month period immediately before oral isotretinoin treatment (to identify whether patients had recently been prescribed conventional therapy before being prescribed oral isotretinoin, as advised in the product labeling) and analyzing the duration of oral isotretinoin treatment.

The first part of the study included 2 cohorts, the "overall acne population" and the "isotretinoin population," which were stratified by gender and age. The primary outcome measures were the number, gender, and age of patients (age was stratified into 4 groups: <17 years, 17-21 years, 22-30 years, and >30 years), and the number of

TABLE 4 Percentage of the Acne Population Who Were Prescribed Oral Isotretinoin and the Average Number of Oral Isotretinoin Prescriptions Per Patient

Year	Overall Acne Population	Patients Who Received Isotretinoin (% of Acne Population)	Average Number of Isotretinoin Prescriptions Per Patient
1997	29,617	3,068 (10.4%)	3.45
1998	43,786	5,135 (11.7%)	3.37
1999	46,843	4,820 (10.3%)	3.31
2000*	54,894	6,174 (11.3%)	3.05

*Year-2000 data extrapolated to full year. (Data were extracted from 1/1/97 to 8/31/00.)

prescriptions for oral isotretinoin.

The first cohort—overall acne population—was defined as all members continuously enrolled throughout each calendar year 1997, 1998, 1999, or January through August 2000 who had been diagnosed with acne vulgaris (ICD-9 code 706.1) or who had received a topical retinoid (tazarotene, tretinoin, or adapalene), topical antibiotic (clindamycin, erythromycin, or sulfacetamide-sulfur), benzoyl peroxide, benzoyl peroxide/erythromycin combination, azelaic acid, oral antibiotic (doxycycline, minocycline, tetracycline, or erythromycin), or oral isotretinoin. Since oral antibiotics have many uses, all patients who qualified on the basis of having received one of the oral antibiotics were also required to have had a diagnosis of acne vulgaris. Patients were excluded from this cohort if they had been diagnosed with mycosis fungoides/cutaneous T-cell lymphoma, rosacea, psoriasis, ichthyosis congenital, White’s disease, or “other dermatoses” (ICD-9 diagnosis code of 757.39) in case oral isotretinoin had been prescribed to treat these conditions rather than acne.¹⁴ (Table 3)

The second cohort—isotretinoin population—consisted of all members who had received isotretinoin and been continuously enrolled with the HMO for the relevant calendar year (1997, 1998, 1999, or January to August 2000). From the pool of members continuously enrolled, isotretinoin utilization was assessed.

Patient Selection to Analyze the Utilization of Other Antiacne Medications

Claims data for the second part of the study were reviewed from July 1, 1997, through July 31, 1999, and patients were required to have been continuously enrolled during this time. Patients were included only if their earliest observed oral isotretinoin prescription occurred during 1998 and they had not had any prescriptions for oral isotretinoin in the preceding 6 months. Thus, the time-span included an index date that fell within the period of January

1, 1998, to December 31, 1998, a 6-month pre-index period prior to the index date, and a 7-month follow-up period after the index date. Patients were excluded if they had been diagnosed with mycosis fungoides/cutaneous T-cell lymphoma, rosacea, psoriasis, ichthyosis congenital, White’s disease, or other dermatoses (in case oral isotretinoin had been prescribed to treat these conditions rather than acne).¹⁴

The prescribing of other antiacne medications in the 6 months preceding the oral isotretinoin prescription was analyzed to evaluate what medications patients had used in the recent past before resorting to oral isotretinoin. In addition, the number of days’ supply of oral isotretinoin in the 210 days (7 months) after the first observed oral isotretinoin prescription was evaluated to ascertain the duration of therapy. This 7-month period was anticipated to include a 4-month to 5-month period of treatment plus a 2-month period off-treatment, as advised in the labeling.

Results

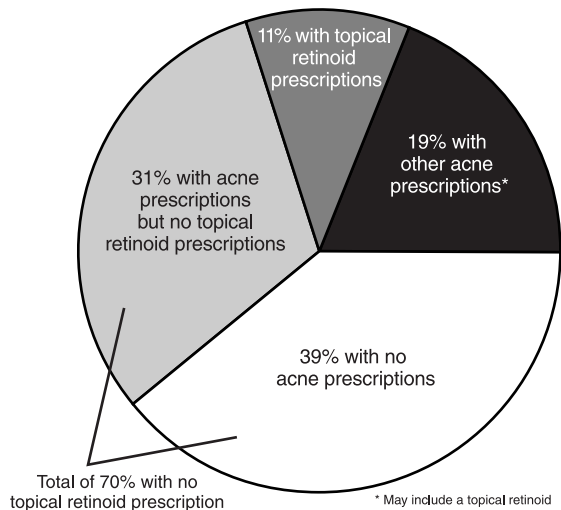
Review of Oral Isotretinoin Utilization

Of approximately 2.08 million members in the database of the HMO, approximately 0.2% received a prescription for oral isotretinoin. The overall utilization of oral isotretinoin and other acne medications in this managed care population in a typical year is depicted in Table 2. The impact of mail-order services on use patterns was not examined in the study since less than 1% of patients used the mail-service pharmacy to obtain acne medications. On average, the number of patients in the “overall acne population” (essentially those using a prescription acne medication or having a diagnosis of acne vulgaris) was 43,783 per year (Table 3 [year-2000 data was extrapolated to full year from 8/31/00]). This excludes an average of 2,696 patients per year who had skin diseases that might be treated with isotretinoin (mycosis fungoides/cutaneous T-cell lymphoma, rosacea, psoriasis, ichthyosis congenital, White’s disease, or other dermatoses) and an average of 6,788 patients per year who were not continuously enrolled during each calendar year.

The percentage of patients in this overall acne population who received at least one prescription for oral isotretinoin within each calendar year remained largely constant from 1997 to 2000 (10.4%, 11.7%, 10.3%, and 11.3% in successive years). Although the number of patients with acne who received isotretinoin and the number of oral isotretinoin prescriptions both increased considerably during this period (from 3,068 in 1997 to 6,174 patients in 2000 and from 10,582 to 18,843 prescriptions [year-2000 data was extrapolated to full year from 8/31/00]), the mean number of oral isotretinoin prescriptions per patient declined from 3.45 to 3.05 (Table 4). Thus, the overall increase in oral isotretinoin prescriptions appears to be attributable to a larger number of patients in the database rather than any increase in relative per-patient usage.

The prescriptions for oral isotretinoin were split almost equally

FIGURE 2 Acne Medication Utilization in the 6 months Immediately Before the First Observed Oral Isotretinoin Prescription



between males (47% to 49%, depending on the year) and females (51% to 53%). The mean ages (\pm SD) were 22 years (\pm 11) for the males and 26 years (\pm 11) for the females. Thus, the vast majority of the female patients were likely to be of childbearing potential.

The average number of prescriptions dispensed per patient was highest in the youngest age group (3.5 for patients less than 17 years) and decreased with age (to 2.9 for patients greater than 30 years). This trend, which was also evident in both the male and female subgroups, may reflect the relatively higher risk of relapse in younger patients that has been reported in the literature.¹⁵

At least 52% of oral isotretinoin prescriptions were written by a dermatologist. Although the remaining prescribers were classified as nondermatologists, some could have been dermatologists using their general practice Drug Enforcement Administration (DEA) number. The mean number of prescriptions per prescriber was higher for dermatologists than for nondermatologists (9.6 ± 3.7 SD versus 4.4 ± 3.7 SD).

Evaluation of Actual Oral Isotretinoin Utilization with Regard to the Product-Labeling Information

There are 1,328 patients included in the cohort for the analysis of patients who were newly started on oral isotretinoin during 1998. "Newly started" was defined by the absence of any prescription claim for oral isotretinoin during the 6-month period before the first prescription for oral isotretinoin. Analysis of patients' utilization of all antiacne medications in the 6 months preceding their first prescription for oral isotretinoin showed that 39% (514) had not received a prescription for any type of antiacne medication and an additional 31% (416) had received at least one prescription

for an antiacne medication but not one for a topical retinoid (Figure 2). Thus, 70% of patients had not received a prescription for a topical retinoid (deemed necessary for "conventional therapy") in the preceding 6 months. Among these 70% of patients, those considered to have been prescribed oral isotretinoin in accordance with the labeling information might include any patients who had been treated with the drug in the past and who were now requiring another course of treatment and any patients with severe nodulocystic disease that had proved to be unresponsive to conventional therapy more than 6 months before their first observed oral isotretinoin prescription. Clinical experience suggests that neither of these scenarios are likely to account for a large proportion of patients in the 70% group, and thus, it would appear that in a sizeable proportion of patients, oral isotretinoin had not been prescribed in accordance with its labeling information.

The product labeling advises that the maximum duration of a course of oral isotretinoin therapy should be 20 weeks. Although, strictly speaking, this is equivalent to 140 days (20×7 days), in practice, patients would likely be given 5 monthly prescriptions, which would be equivalent to 150 days (5×30 days). Evaluation of the number of days' supply of oral isotretinoin dispensed in the 210 days following the initial prescription for the drug revealed that 27% of patients had received more than a 150-day supply of oral isotretinoin, and 23% of all patients had received more than a 180-day supply (equivalent to 6 monthly prescriptions). Furthermore, 14% of patients had received more than a 200-day supply. These data suggest that a significant proportion of patients are being prescribed courses of oral isotretinoin that are longer than those advised in the product labeling.

Limitations

There are several factors that should be considered when interpreting these data. Some of the observed isotretinoin use may be at least partially attributable to physicians using their clinical experience and judgment to prescribe in the manner that they consider to be in the best interest of each patient. In addition, the use of oral isotretinoin could have been affected by prior authorization policies for topical retinoids intended to prevent reimbursement of these medications when prescribed for the treatment of photo-damage rather than acne. Prior authorization (PA) policies were in effect for topical tazarotene and adapalene and in patients aged 25 or older (aged 35 in some cases) for topical tretinoin. Among the prescription claims for topical tretinoin that required prior authorization, approximately 14.1%, 11.4%, and 10.3% were denied during calendar year 1998, 1999, and 2000, respectively. These PA restrictions on step therapies meant to precede oral isotretinoin might have had unintended consequences in discouraging precursor therapy or, if patients decided to pay the full cost of the topical tretinoin or other topical retinoid themselves, it might have led to underreporting of topical retinoid use. Furthermore, the extent of inappropriate prescribing of oral isotretinoin after denial of topical tretinoin could not be determined from the database. Future

studies in these areas may be necessary to further understand prescribing behavior and medication utilization for the treatment of acne in order to optimize clinical, economic, and humanistic outcomes for these patients.

Conclusions

The issue of whether, and when, to prescribe oral isotretinoin for a particular patient should be a joint decision between the physician and patient. The decision should consider safety, efficacy, cost, and patient acceptability, with safety being a particularly important issue with oral isotretinoin. Although undoubtedly of great clinical value, the drug causes birth defects in women who become pregnant during therapy. Pregnancies in patients taking isotretinoin occur despite the existence of strongly worded warnings in the labeling information and extensive education initiatives directed at both physicians and patients.

It appears that none of the 3 main prescribing requirements included in the labeling information for oral isotretinoin are being adhered to strictly. Market research data reveal that approximately 37% of oral isotretinoin use in acne is in patients with only mild or moderate acne,¹³ and the results of this study reveal that up to 70% of patients may not have received a trial of a topical retinoid (and, therefore, conventional therapy) prior to receiving oral isotretinoin, and up to 27% of patients may be prescribed a course of therapy longer than 20 weeks.

DISCLOSURES

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Author Kristina Chen served as principal investigator and author of the study. Study concept and design were contributed primarily by White and Chen. Analysis and interpretation of data were contributed primarily by Chen. Drafting of the manuscript was primarily the work of Chen. Critical revision of the manuscript was primarily the work of Chen and White. Statistical expertise was contributed primarily by author Eunice Chang. Administrative, technical, and/or material support was provided by Prescription Solutions.

REFERENCES

1. Wolff HH, Plewig G, Braun-Falco O. Ultrastructure of human sebaceous follicles and comedones following treatment with vitamin A acid. *Acta Derm Venereol* 1975;74(suppl):99-110.
2. Committee on Guidelines of Care for Acne Vulgaris. *J Am Acad Dermatol*. 1990;22:676-80.
3. Maddin WS, Landells IDR, Poulin Y, et al. Treatment of acne vulgaris and prevention of acne scarring: Canadian Consensus Guidelines. *J Cutan Med Surg*. 2000;4(suppl 1):S2-S13.
4. Product labeling for isotretinoin. *Physicians Desk Reference*, 55th ed. Montvale, NJ: Medical Economics Company, Inc.; 2001.
5. Meigel WN. How safe is oral isotretinoin? *Dermatology*. 1997;195(suppl 1): 22-28; discussion 38-40.
6. Scheinman PL, Peck GL, Rubinow DR, et al. Acute depression from isotretinoin. *J Am Acad Dermatol*. 1990;22:1112-14.
7. Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol*. 2000;136:1231-36.
8. Wysowski DK. Methodological limitations of the study "Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide." *Arch Dermatol*. 2001;137:1102-03.
9. House Accutane safety hearing will include testimony from FDA's Woodcock. *Pink Sheet* 62 (No 49), Chevy Chase, MD: F-D-C Reports Inc.; Dec. 4, 2000.
10. Perlman SE, Leach EE, Dominguez L, et al. Be smart, be safe, be sure. The revised Pregnancy Prevention Program for women on isotretinoin. *J Reprod Med*. 2001; 46(suppl 2):179-85.
11. Accutane-exposed pregnancies—California, 1999. *MMWR Morb Mortal Wkly Rep*. 2000;49:28-31.
12. Autret-Leca E, Jonville-Béra AP, Szafir D, et al. Roaccutane chez la femme en âge de procréer: étude de l'impact du renforcement des recommandations de prescription. *Ann Dermatol Venereol*. 2000;127:808-13.
13. Physician Drug and Diagnosis Audit (PDDA), January 1996-December 2000. Newton, PA: Scott-Levin, Inc. [Based on Accutane PDDA drug usage for acne (Dx 706.1) by severity, patient sex, and patient age for the years 1996-2000. Unspecified data excluded. Severity based on physician perception and not on clinical guidelines.]
14. *Drug Facts and Comparisons*. 55th ed. St. Louis, MO: Facts and Comparisons; 2001.
15. Lehucher-Ceyrac D, de La Salmoniere P, Chastang C, Moreng P. Predictive factors for failure of isotretinoin treatment in acne patients: results from a cohort of 237 patients. *Dermatology*. 1999;198:278-83.