Appendix 4
Stern Analysis of Medication and Medical Service Utilization for Acne

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Medication and Medical Service Utilization for Acne: 1995-1998

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Background:

Acne occurs in most persons sometime during adolescence or early adulthood and is a frequent reason for visits to dermatologists and for prescription drug therapy.

Objective:

To analyze changes in the utilization of physician services and medications for the treatment of acne.

Methods:

We analyzed data from two United States federal surveys of outpatient physician services and prescribing for the years 1980 to 1997 and two commercial sources of drug prescription data for 1996 to 1998. From these data, we estimated visits for acne and drugs prescribed during these visits.

Results:

Visits for women principally for acne are about 80% more frequent than those for men. Each year 5 million prescriptions for oral antibiotics and 1.4 million prescriptions for isotretinoin are dispensed for the treatment of acne.

Conclusion:

Substantial health care resources are devoted to the treatment of acne, with women particularly likely to continue to frequently utilize these services after age 19.

INTRODUCTION

Acne is the single most common reason persons ages 15 to 45 visit a dermatologist[1]. Although the prevalence of acne is higher among men than women, past studies and clinical experience indicate that woman are more likely than men to seek medical care for the treatment of acne[1,2]. At some time during adolescence or as adults, the majority of men and women have acne. By age 18, as many as one-fourth of adolescents will have scarring attributed to acne[3]. Our previous work based on a Federal Survey has documented the utilization of office based ambulatory physician services for the treatment of acne up to 1991[1]. Current available data from this survey and data from another Federal Survey provide information on utilization of medical services in office and hospital based ambulatory practice in the United States for acne through 1997.

Since the 1950's IMS America has conducted surveys of drug prescriptions and utilization. The National Disease and Therapeutic Index (NDTI) has collected data about prescription treatment provided by office based physicians in the United States. IMS America also conducts the National Prescription Audit (NPA), a study of drugs dispensed at retail pharmacies. These sources of data provide estimates of the utilization of medical resources for the treatment of acne, particularly the use of prescription drugs, and together provide an assessment of long term trends in the pattern of acne visits, including the type of physicians

who provide care, the types of medications currently prescribed for this indication, and the characteristics of persons seeking care for acne.

MATERIALS and METHODS

We utilized two primary Federal data sources and two IMS surveys. The National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey Outpatient Department (NHAMCS-OPD) are Federal surveys meant to document care provided to outpatients[4,5]. The National Ambulatory Medical Care Survey utilizes a multi-stage probability design involving primary sampling units consisting of physician practices and patient visits within physician practices to assess reasons for visit, diagnosis for the visit, demographic and prescription information for patients who obtain services from physicians in non-institutional (ie. office based) ambulatory practice. This survey has been conducted periodically from 1974 to 1985 and annually since 1989. As of September 30, 1999 the most recent survey year data available to the public was for 1997. Since 1980, prescription data has been collected as part of this survey. Typically, this survey samples between 25,000 and 50,000 office visits each year.

Both the NAMCS and the NHAMCS OPD surveys share common characteristics[4,5]. Up to three patient reasons for the visit and three physician diagnoses can be coded for each visit. The National Center for Health Statistics has developed a codebook to categorize patient complaints[6]. Acne has a specific code. For physician's diagnosis, ICDA-9-CM Code 706.1 is the code for acne vulgaris and conglobata[7]. This code includes the diagnosis of severe

recalcitrant nodular acne. The first listed patient complaint and first listed diagnosis reflect the principal reason for a visit. In our analysis, unless otherwise specified, visits with acne as the principle visit as well as when specified, all visits with acne listed as patient's reason for a visit (ie. first or other) or with the physician's diagnosis acne (as the primary or other diagnosis for this visit) are considered.

We categorized the 200 most frequently mentioned drugs in the NAMCS listed as prescribed during visits principally for acne as likely to be oral or injectable agents for the treatment of acne or as topical preparations or as agents more likely to be prescribed for an indication other than acne[8]. We also quantified the number of visits for acne as any complaints, with Tetracyclines of any of three types (ie. Doxycycline, Tetracycline or Minocycline) prescribed. The specialty of the physician seen (dermatologist or other) and if this was a first or subsequent visit to this practitioner for acne was also quantified.

To gain statistical precision we combined data for consecutive two-year periods, except 1985 for which no survey was conducted in the year prior or subsequent and for the most recent three years (1995-1997), which we considered together. Because this is a multi-stage probability sample, each patient's visit is assigned a weight by the NCHS. On the basis of these weights, it is possible to estimate the number of visits of a specific type for the United States. In general, when two years' data are considered together, estimates of more than 500,000 visits

per year have reasonable relative standard errors generally on the order of 15 to 30 percent. The magnitude of the relative standard error decreases as the estimate increases; standard errors vary with year, if the data is for visit to physicians in one specialty or to all physicians, and if the data concerns drug mentions or physician visits. In general, estimates of physician visits have smaller relative standard errors than estimates of prescriptions. Data concerning visits to physicians with a specific specialty have lower standard errors than those for equal estimates of visits to all types of physicians.

In addition to analyzing data from the NAMCS, we also obtained and analyzed data from the National Hospital Ambulatory Medical Care Survey for the years 1995-1997[5]. Since the National Hospital Ambulatory Medical Care Survey data we analyzed are limited to hospital based outpatient departments of general and short stay hospitals exclusive of federal, military and Veteran's Administration hospitals, the data from both federal surveys we analyzed excludes services provided for dermatologic disease by a variety of providers including those located in community-based clinics. Therefore, the data presented here provided only a partial assessment of the full scope of medical care provided in the treatment of acne. We considered results of the NHAMCS-OPD survey separately from those of the NAMCS.

IMS America (Towota, NJ Campus) is a for profit company that conducts surveys of drug prescribing and utilization. I utilized data provided by IMS from the NDTI,

including estimates of the number of visits with a physician diagnosis of acne (ICDA 9-CM code=706.1) each year by sex, and according to whether this was a first or subsequent visit to that office based practitioner for surveys conducted from 1996 to 1998. Survey estimates of the number of visits with a drug prescribed or mentioned for the 20 most frequently prescribed medications at visits for acne were also analyzed. Each drug was classified according to name and not chemical class. Therefore, brand name(s) and generic names were considered separately in the data provided. As a result, with combination agents counted separately, the top 20 named medications prescribed at acne visits represent 13 distinct chemical entities (or distinct combination dosage forms). In this analysis, all orally administered dosage forms among the 20 most frequently prescribed drugs for acne were aggregated according to generic name (ie. Minocycline included Dynacin, Minocin and generic Minocycline).

The number of visits with a prescription or mention of any of four most commonly prescribed oral antibiotics for acne (Minocycline, Tetracycline (including Sumycin) and Erythromycin-base (oral) and Doxycycline (including Monodox)) was also tabulated. These medicines are sold under other brand names as well. Erythromycin is available in many forms and is used both topically and orally. Therefore, for this class of drugs, only erythromycin base data were included in tabulations of oral antibiotics use. In addition, the totals presented are restricted to commonly used drugs and underestimate total oral antibiotic use for the treatment of acne. Because of the limited size of the NDTI sample, relative

standard errors for estimates provided in this report are likely to be substantial. Relative standard errors or methods for estimating these errors for the various strata were not provided to me by IMS.

The NPA surveys a large number of pharmacies and determines the number of prescriptions dispensed by drug name, with each brand or generic name considered separately. It classifies prescriptions in two ways: 1. New prescriptions are defined as those that are the result of a specific new action on the part of the dispensing physician ie. a new written or telephone prescription is provided for that patient to that pharmacy. Therefore, new prescriptions do not necessarily indicate that a given patient is using this drug for the first time. For a new prescription to be coded, a direct interaction between the prescribing health professional and the pharmacy (often involving patient interaction with the prescriber) to provide a new supply of a drug should have occurred. 2. Refill prescriptions are prescriptions that are refilled on the basis of pre-authorized refills from the original prescribing health professional without any need for new interaction between pharmacy and prescriber (ie. no new physical prescription or called in prescription was provided). The NPA does not collect the data on reason a prescription was dispensed. Because many medications, particularly oral antibiotics, are utilized for many reasons, to estimate the number of prescriptions for each of the top 20 agents for acne as tabulated by IMS we estimated usage for acne using NDTI estimates of the proportion of all visits associated with a specific drug that were for acne. This proportion was then

multiplied by total NDA estimated prescriptions for each drug. For example, in 1996 the NDTI estimate that 97% of all visits with an isotretinoin prescription were for acne. The data we utilized does not permit us to assess the proportion of visits with an isotretinoin prescription that are for severe recalcitrant cystic acne, the current indication for this drug in the United States[9]. This weight was used to estimate the proportion of isotretinoin prescriptions dispensed in pharmacies as recorded in the NPA survey that were for acne. In contrast, only 7% of erythromycin base prescriptions in the 1996 NDTI were associated with a diagnosis of acne. This percentage was applied to the overall NDA estimate of total prescriptions of that year to estimate the number of prescriptions of erythromycin base filled for acne. Formulas for estimating standard error were not provided for the NPA by IMS, but given the large sample size of the NPA; the estimates of the number of prescriptions are likely to have relatively low standard error. Because we used NDTI findings to estimate the proportion of total prescriptions for acne, the precision of such estimates has a larger standard error, particularly for medicines often utilized for indications other than acne.

RESULTS

Visits for Acne

According to NAMCS data, during each survey year since 1985 there have been from 6.5 to 7.5 million visits to office based physicians listed with acne as a reason for the visit or as a physician diagnosis (Table 1). Each year from 5 to 6 million visits are made to physicians in outpatient office practice with acne (ICDA Code = 706.1 Reason for Visit Code = 1830) as the principle reason or primary diagnosis. Women account for approximately 65% of visits with a principle diagnosis or reason of acne. In this Federal survey from 1995 to 1997, there were an average of 3,300,000 visits to physicians in office based practice per year by women with the principle reason or diagnosis of acne and more than four million visits per year by women with acne as a specifically listed diagnosis or reason. NDTI estimates of total visits for acne to office based practitioners 1996 to 1998 were quite consistent with NAMCS estimates, averaging 6.2 million visits per year. The number of visits per year increased slightly from 1996 (5.9 million) to 1998 (6.7 million). Both the NAMCS and NDTI estimate 3.7 million visits for acne by women in 1996. Overall, the percent of all acne visits made by women were remarkably consistent between the two surveys for the years in common (63% NDTI vs. 65% NAMCS). According to the NDTI survey, approximately 37% of all visits by both men and women from 1996 to 1998 were first visits to

that practitioner for that complaint; higher than the 27% estimate of the National Ambulatory Medical Care Survey.

Table 2 provides the percentage age and sex distribution of the more than 6 million visits per year to outpatient physicians for acne for both the NAMCS (1995-97) and for the NDTI (1996-98). Women age 20 and older accounted for the majority of visits by women. Only about one fourth of visits by men for acne were accounted for by this age group. On average, the women making visits principally for acne from 1995 to 1997 were nearly five years older than the men (mean 26.2 vs. 21.4 for women and men, respectively $P<.001$, NAMCS data). Since 1980, the mean age of patients making outpatient visits with a primary reason of acne or primary diagnosis of acne had increased for women (from an average age at visit of 23.6 in 1980-1981 to 26.2 by 1995-1996), but not for men (average age 21.2 in 1980-1981 versus 21.4 in 1995-1996). The visit rate for acne (visits per 100,000 person years) among women age 20 and older is about threefold higher than for men.

According to NAMCS, about 24% of persons visiting a physician primarily for acne had not seen this physician for this problem before. The NDTI notes a higher proportion (nearly 40%) of acne visits that are first visits to that practitioner. In both surveys, an approximately equal proportion of men and women were seeing that physician for the first time. According to NAMCS data, the percentage of visits for acne that were first visits to a physician for that complaint have been relatively constant since 1990, and that percentage was

higher from 1990 to 1997 than in earlier years (1980-1985) (>25% vs. 20%, respectively).

Prescribing for Acne

In the three most recent years of both surveys, a prescription for an oral or injectable agent likely to be used for acne was provided at the majority of visits to physicians primarily for acne. Men were slightly more likely than women to be given a prescription for a systemic acne agent. According to NAMCS, from 1985 to 1997, the proportion of men and women who visited a physician primarily for acne who were treated with an oral or injectable agent varied little (maximum inter-year difference 3%). In the three most recent years of both the NAMCS and NDTI surveys, women average more than 1.7 million visits per year to physicians in the office based practice for acne that included the prescription of oral antibiotics or isotretinoin. The NAMCS estimate that at first visits for acne, 40% of women are prescribed systemic therapy, with oral antibiotics accounting for over 90% of these prescriptions and isotretinoin for less than 5%. According to NDTI data, there was an average of 1.6 prescriptions per visit for acne. The number of prescriptions per visit was nearly identical for men and women. Women received more than 6.1 million prescriptions and men 3.8 million prescriptions per year for acne treatment. The 20 most frequently prescribed agents for acne accounted for approximately 75% of all prescriptions for acne recorded by the NDTI from 1996 to 1998.

Of the top 20 medications prescribed for acne, eight were specifically named oral antibiotics. Overall these eight specific oral antibiotics were prescribed at an average of 2.3 million visits per year. At 34% of visits by women for acne, one of these specific eight antibiotics was dispensed. NDTI and NAMCS estimates of oral antibiotic usage are consistent. According to the NAMCS, tetracyclines were prescribed to women seeking care for acne at nearly one million visits per year, including 374,000 visits each year with a prescription of minocycline, 400,000 with a prescription of tetracycline and 215,000 visits with a prescription of doxycycline.

In 1985, the first NAMCS survey year after the 1982 introduction of isotretinoin into the United States market, visits with a prescription for isotretinoin totalled about 400,000. In the most recent three years (1995-1997), the number of visits with an isotretinoin prescription had increased to 740,000 per year, an 82% increase. Possible reasons for this increase are detailed in the discussion. The increases in the number of visits with isotretinoin prescribed was about equal in men and women (Table 3). Although visits per year with an isotretinoin prescription are about equal for men and women, a higher proportion of visits principally for acne by men (19%) included a prescription for isotretinoin than was the case for women (12%).

NDTI estimates of the number of visits with the prescription of isotretinoin are

generally consistent with NAMCS estimates. The NDTI estimates of isotretinoin prescriptions are equal for men and women (about 400,000 visits per year for each sex). The NDTI also indicates a substantially higher proportion of visits for acne by men (16.8%) than by women (10.6%) included an isotretinoin prescription in the most recent three years. From 1995 to 1998, women had 3.5 visits with a prescription of the eight most commonly used oral antibiotics for acne for every visit with a prescription of isotretinoin. For men this ratio was approximately 2.5 to 1.

The National Drug Audit quantifies prescriptions dispensed either as new prescriptions (defined as a new written or telephone prescription, which may still represent continuation of therapy) or renewal prescriptions (ie. refill without any new action by the prescriber). The ratio of new to refill prescriptions is much higher for isotretinoin than for oral antibiotics prescribed for acne (Table 4). In total, NDA data estimates suggest more than 5 million prescriptions each year for the eight most frequently prescribed oral antibiotics for acne, about three and a half times the number of isotretinoin prescriptions.

NAMCS data indicate that the proportion of all visits primarily for acne that were made to dermatologists has declined over time, from 92% in 1980 to 79% in 1996. Women and men are about equally likely to rely on dermatologists for the care of their acne. Among women age 20-34, acne is a particularly frequent reason for visiting a physician, with acne as the fifth most frequent primary

diagnosis given (of 553 diagnoses listed), and the primary diagnosis for 1.33 percent of all visits to office based physicians by women of these ages.

According to the NHAMCS from 1995-1997, there were an additional 200,000 visits per year to hospital outpatient departments located in acute non-federal hospitals with acne as the principle reason or diagnosis for that visit. Because of high relative standard errors in this data sample, further subgroup analysis is not statistically meaningful and was not performed.

DISCUSSION

Because of possible biases in survey sampling as well as statistical power, the accuracy of estimates from even large surveys are sometimes questioned. In prior studies we examined visits for acne up to 1991, using a single federal survey, the National Ambulatory Care Survey[1]. In this analysis, we have been able to update data on acne care from 1991 to 1997 from this survey and also provide estimates from another federal survey as well as two independent commercial surveys, which sample visits to physician and prescriptions for many indications, including acne. That these independent estimates are so consistent is a strong argument that the findings presented here concerning the utilization of physician services and prescribing for acne are accurate.

According to both the federal and the commercial surveys of physicians in outpatient practice, acne remains one of the most frequent reasons for visits to a dermatologist, with 5 to 6 million visits per year principally for this reason, and total visits with acne as a diagnosis in excess of 7 million per year since 1995. Hundreds of thousands of additional patients are also likely to seek care for acne from clinics, hospital outpatient departments, and other sources. In addition, many affected individuals do not receive care from physicians.

For every three visits by men for this reason there are about five visits by women. More notable is the difference in the age distribution between men and

women who seek care for acne. The majority of women seeking care for acne are age 20 or older. In contrast, more than two-thirds of males who seek physician's care for acne are less than age twenty. For every visit by a male over age twenty, there were nearly four visits by females in this age group for the treatment of acne suggesting that many women past teenage years perceive acne as a continuing problem that is sufficiently severe to warrant medical attention.

Each year more than 5 million prescriptions for oral antibiotics are dispensed. These prescriptions represent both new and refill prescriptions resulting from the more than 2 million visits per year at which such agents are prescribed. Women account for the majority of prescriptions for oral antibiotics dispensed to treat acne. In addition to oral antibiotics, hormonal therapies are often prescribed at visits by women for acne. These agents, including oral contraceptives, may be primarily for the treatment of acne or may be primarily for contraception.

Since 1985, during all but two of the survey years, the number of visits by men and women with isotretinoin prescribed was nearly equal. During 1991-92 visits, isotretinoin prescriptions for males were about twice those for women and were substantially increased compared to prior years. Numbers of isotretinoin prescriptions for women did not increase until 1993. This difference in the timing of the increase in isotretinoin prescribing might be due to the heightened concerns about isotretinoin associated embryopathy, if fetal exposure occurs,

and the initiation of the Pregnancy Prevention Program in the late 1980s and early 1990s[10,11,12].

From 1995 to 1998, both the number of prescriptions of isotretinoin dispensed and visits with isotretinoin prescribed were equal for men and women. Men ages 19 and younger accounted for more than two-thirds of all visits with isotretinoin prescribed to men, but more than 70% of women prescribed isotretinoin were age 20 and older. These data are consistent with the reported higher prevalence of clinical acne in older women than in men[13]. Also, physicians may reserve this therapy for older women, whom they may believe to be more likely to adhere to the Pregnancy Prevention Program.

Since 1985, the number of visits for acne has increased only modestly, but the proportion of visits with an isotretinoin prescription has approximately doubled for both women and men. A number of factors including those discussed here, might help to explain the increased prescribing of isotretinoin. First, isotretinoin is an expensive drug. In the last decade the number of persons with health insurance that includes a prescription benefit that would defer most of this cost has increased substantially. This decreases possible financial barriers to treatment. Second, the therapeutic benefits of isotretinoin are probably even more widely known now than they were before 1990. Third, as clinical experience increased with this agent, both patient demand and physician knowledge with its prescribing may have increased.

The changes in the prescribing of isotretinoin over time are comparable between genders. Since 1985, the proportion of visits for acne with an isotretinoin prescription has been consistently higher for men than women. This finding is consistent with a higher prevalence of severe acne among males[1]. Our data do not permit us to assess the extent to which prescribing in either gender follows patient package recommendation or the extent to which there is adherence to the Pregnancy Prevention Program's[11].

According to its labeling, isotretinoin should be administered for a 15 to 20 week course, which typically leads to prolonged remissions of severe recalcitrant acne[14]. Oral antibiotics may suppress acne but are unlikely to induce prolonged remissions, suggesting the duration of use is often far longer for oral antibiotics than isotretinoin. Yet, the ratio of prescriptions that involved direct physician interaction, defined as new prescriptions, is substantially higher for isotretinoin than oral antibiotics used for acne. This finding is consistent with close physician supervision of patients during isotretinoin therapy and frequent refills of oral antibiotics prescriptions without patient physician interactions when these antibiotics are being used to treat acne. From 1974 to 1991, there was a substantial decrease in reliance on dermatologists for the treatment of acne[15]. Since 1991, dermatologists have maintained a constant share of visits primarily for acne (about 80%), suggesting that this specialty continues to be regarded as the primary source for acne therapy. Overall, dermatologists account for about 85% of isotretinoin prescriptions.

Clearly acne is a substantial problem, which causes patients to initiate millions of visits per year to physicians and with total cost of acne likely to exceed a billion dollars. We lack data that comprehensively assesses physical, psychological and economic impact of acne on individuals or assures us that guidelines that are meant to optimize rational prescribing for acne are being followed.

TABLE 1

NAMCS Estimates of Visits (Thousands per Year) to Office Based Physicians for Acne (Overall and Only as Primary Reason or Diagnosis) by Year and Sex

	Female		Male	
Years	All Acne	Primary Reason	All Acne	Primary Reason
1980-81	5740	5051	3347	3117
1985	3864	3381	2599	2263
1989-90	4620	3596	2637	2191
1991-92	4936	3741	2817	2488
1993-94	5064	4045	2705	2289
1995-97	4393	3280	2350	1805

TABLE 2

Age Distribution (Percent) of Visits for Acne by Sex According to the NAMCS (1995-97) and NDTI (1996-98)

Age	Female		Male	
	NAMCS	***NDTI***	***NAMCS***	***NDTI***
10-19	33	43	67	71
20-39	51	43	25	21
40-59	16	9	9	4
Total	100	100	100	100

*Excludes visits with age and/or sex not specified or < 10 or >59 (about 5% of all acne visits).

TABLE 3

NAMCS Estimates Number (Thousands per Year) (and Percent) of Visits for Acne (as Primary Reason) with Accutane Prescription Listed by Year and Sex

Year	Female	Male
1980-1981	*	*
1985	189 (5.6)	218 (9.6)
1989-90	150 (4.3)	216 (9.9)
1991-92	210 (5.3)	459 (18.4)
1993-94	404 (10.0)	335 (14.6)
1995-97	406 (12.4)	334 (18.6)

*Isotretinoin first licensed in 1982.

TABLE 4

NPA Estimates of New* and Renewal Prescriptions per Year (Thousands) for Selected Oral Antibiotics and Accutane for the Treatment of Acne by Sex, 1996-1998**

	Female			Male		
Medication	***New***	***Renewal***	***Total***	***New***	***Renewal***	***Total***
Oral Antibiotics	1780	1096	2875	1390	830	2220
Accutane	581	142	723	565	137	702

*New written or telephone prescription (see Methods)

**See Table 3 footnotes for antibiotics included in tabulation

Bibliography

1. Stern RS. Acne therapy. Medications use and sources of acre in office-based practice. *Arch Dermatol* 1996;132:776-80.
2. Stern RS. The prevalence of acne on the basis of physical examination. *J Am Acad Dermatol* 1992;26:931-5.
3. Kilkenny M, Merlin K, Plunkett A, Marks R. The Prevalence of common skin conditions in Australian school students: 3. Acne vulgaris. *Br J Dermatol* 1998;139:840-845.
4. Tenney JB, White KL, Williamson JW. National Ambulatory Medical Care Survey: background and methodology. *National Center for Health Statistics Vital Health Stat* 1974;2.
5. McCaig LF, McLemore T. Plan and operation of the National Hospital Ambulatory Medical care Survey. *National Center for Health Statistics Vital and Health Stat* 1994;1.
6. Schneider D, Appleton L, McLemore T. A reason for visit classification for ambulatory care. *National Center for Health Statistics Vital Health Stat.* 1979;2.
7. *International Classification of Diseases*, 9th Revision, *Clinical Modification.* Fifth Edition. Salt Lake City: Medicode Publicatons, 1996.
8. Koch H, Campbell W. The collection and processing of drug information. National Ambulatory Medical Care survey, 1980. *National Center for Health Statistics Vital Health and Stat* 1982;2.

9. Accutane. In: PDR, 53rd Edition. Montvale (NJ): Medical Economics Co.; 1998. P.2651-2653.

10. Stern RS. When a uniquely effective drug is teratogenic. The case of isotretinoin. *N Engl J Med* 1989;320:1007-9.

11. Mitchell AA, Van Bennekom CM, Louik C. A pregnancy-prevention program in women of childbearing age receiving isotretinoin. *N Engl J Med* 1995;333:101-6.

12. Dai WS, Hsu MA, Itri LM. Safety of pregnancy after discontinuation of isotretinoin. *Arch Dermatol* 1989;125:362-5.

13. Goulden V, Stables GI, Cunliffe WJ. Prevalence of facial acne in adults. *J Am Acad Dermatol* 1999;41:577-80.

14. Lehucher-Cyrac D, Webber-Buisset MJ. Isotretinoin and acne in practice: a prospective analysis of 188 cases over 9 years. *Dermatology* 1993;186:123-8.

15. Stern RS. Managed care and the treatment of skin diseases. Dermatologists do it less often. *Arch Dermatol* 1996;132:1039-42.