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Effective monitoring of isotretinoin safety in a pediatric dermatology population: A novel “patient symptom survey” approach

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Abstract

Background—Assessment of adverse effects in pediatric patients on oral isotretinoin has not been standardized and the exact incidence is unknown.

Objective—Our goal was to determine the utility of an isotretinoin symptom survey (ISS) as a screening tool for assessment and quantification of adverse effects, including psychiatric symptoms, during isotretinoin treatment in a pediatric population of different age groups.

Methods—We performed a retrospective chart review on a random sample of patients treated with isotretinoin at a tertiary pediatric dermatology clinic where patients completed an ISS at each visit. Responses were stratified by age group and prior psychiatric history.

Results—The charts of 102 patients, representing 123 courses of isotretinoin and 760 treatment months, were reviewed. Seven hundred and twenty-two (95.0%) symptom surveys were complete and 38 (5.0%) were incomplete/missing. Recorded side effects were similar to published adult data; dry lips/dry skin were reported in 94.25% and 72.13% treatment-months of isotretinoin, respectively. Psychiatric symptoms were reported in 1.65%, with no statistical difference between patients with or without a prior mental health history. Patients aged 11–15 years had similar side

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effect profiles to those aged 16–21. Impaired night vision, nosebleeds, and dry/bloodshot eyes were more common in the older age group.

Limitations—This was a retrospective chart review, with known limitations. The study was performed at a tertiary referral center for pediatric dermatology, possibly allowing patient selection bias.

Conclusions—The ISS appears to be an effective screening tool to standardize monitoring of isotretinoin side effects in the pediatric population.

Introduction

The efficacy of oral isotretinoin as a treatment for severe acne is well documented.^{1–4} Adverse effects, particularly teratogenicity, and concerns regarding depression limit the degree of comfort with which it is used in the pediatric population.^{5–8} The high risk for teratogenicity has led to implementation of strict pregnancy prevention policies and programs.^{5,9} Frequent side effects include cheilitis and xerosis, which usually respond well to liberal use of emollients.¹⁰ The psychological effects of isotretinoin are less well understood.^{11–12} In 1998, the United States Food and Drug Administration (FDA) issued a warning of a possible association with depression, psychosis, suicidal ideation and suicide, and recommended the use of signed informed consent forms and printed patient medication guides. It is uncertain if isotretinoin is directly responsible for causing depression as conflicting reports in the medical literature are based on studies using differing research methodologies.^{13–21} One cohort study found that treatment of acne with isotretinoin was associated with a *decrease* in depressive symptoms.²² Confounding factors such as mood changes associated with adolescence and puberty complicate the interpretation of data.^{23,24}

This study examined data from a representative sample of patients attending a pediatric dermatology clinic to assess the incidence and severity of adverse effects and to test the usefulness of a self-reported isotretinoin symptom survey (ISS) as a standardized screening tool.

Methods

A retrospective chart review was conducted on a random sample of patients, who were prescribed isotretinoin at the pediatric dermatology clinic between February, 2003 and August, 2007. The study was approved by the institutional review board of Rady Children's Hospital/University of California-San Diego (protocol #070858).

The ISS (Fig 1) was designed to assess the presence or absence of 13 possible adverse effects: dry lips, dry/bloodshot eyes, dry skin, muscle aches/pains, nosebleeds, frequent headaches, mood swings, depression, suicidal thoughts, paronychia, rash, trouble with night vision, and severe sun sensitivity/sunburn. Additionally, it assessed the severity on a 'mild/moderate/severe' scale of symptoms predicted to be the most common: dry lips, dry/bloodshot eyes, dry skin, muscle aches/pains. The clinic staff instructed patients to complete an ISS at each monthly follow-up visit, with or without the assistance of a family member.

The treating physician reviewed the survey with the patient, and verified the clinical relevance of reported symptoms. The surveys were retained with the patient's chart.

The data were tabulated using a worksheet that included epidemiological information, symptom onset and duration, prior medical history, and age at the beginning of treatment. The patient-completed survey was assessed for its utility in identifying and monitoring adverse effects of isotretinoin as they occurred. The overall incidence and statistical significance of each adverse effect was evaluated. The number of patients who experienced psychological symptoms was determined, as well as the average number of months they experienced such symptoms, and we assessed whether a prior history of a psychiatric condition was of significance. Data from all monthly appointments were aggregated to determine the incidence of each symptom. Confidence intervals for each symptom were calculated.

The data were stratified into two age groups, representing the pediatric and young adult patient populations: "Age 11 – 15" and "Age 16 – 21." The incidence of symptoms for the two age groups was compared using a two-proportion z-test with unequal variances. The calculations assumed an approximately normal distribution, because each individual sample included at least 350 months of data.

Results

The sample size was 102 individual patients, with 123 courses of isotretinoin. There were 760 patient-months of collected data. Of the 123 documented courses of isotretinoin, 73 patients (59.3%) were male and 50 (40.7%) were female. The age range was 11 to 21 years, with an average age of 15.26 years and a standard deviation of 1.62. There were 722 (95.0%) complete symptom surveys, 30 (3.95%) with incomplete data entry, and only 8 (1.05%) unsubmitted surveys (Table I).

The incidence of symptoms is demonstrated in Table II, and in Fig 2. The 95% confidence intervals for the incidence of each symptom are demonstrated in Table III.

Psychological Symptoms

Of 729 survey responses, representing 102 individuals with surveys filled out monthly for the course of treatment, only 12 (1.65%) reported depression, 57 (7.82%) reported mood swings, and 0 (0.0%) reported suicidal thoughts. The 12 surveys with self-reported "depression" represented 11/102 (10.78%) patients. The average onset for symptoms of depression was month 3.27 (standard deviation 1.62), with an average duration of 1.09 months (standard deviation 0.30). Mood swings were reported in 26/102 (25.49%) patients. The average onset for symptoms, in those patients who reported mood swings, was month 1.96 (standard deviation 1.40), with an average duration of 2.19 months (standard deviation 1.63). Overall, 29/102 (28.43%) individual patients reported experiencing depression, mood swings, or both during treatment. By standard practice, reporting of "depression" on the symptom survey prompted a physician evaluation for major signs and symptoms of depression and, as appropriate, psychiatric consultation and/or discontinuation of

medication. In almost every case, self-reported “depression” was not diagnosed to be true clinical depression after thorough evaluation, but more consistent with mood swings.

A small number of patients (12/102) had a prior history of diagnosed psychiatric conditions. There were 4/102 (3.92%) patients with a history of depression before beginning treatment. Only 1 of these 4 patients reported experiencing psychological symptoms while taking isotretinoin: one month of mood swings and one month of depression, both in the sixth month of treatment. One of 102 (0.98%) respondents had a prior history of mood swings, but this patient did not report psychological symptoms during treatment. Eight of 102 (7.84%) patients had a prior history of other psychiatric conditions: attention deficit hyperactivity disorder (ADHD) (6); bipolar disorder (1); and “other” (a history of violence/assault) (1). Only 1 patient (with ADHD), reported psychological symptoms: two months of mood swings, occurring in the second and fourth months of treatment. In total, 2/12 (16.67%) patients with a prior history of a psychiatric condition reported experiencing psychological symptoms while on isotretinoin. These 12 patients completed 83 total months of treatment and psychological symptoms were reported in 4/83 months (4.82%). In only 1/83 months (1.20%) was “depression” reported, suggesting a low incidence of depression in our small sample of patients with a prior psychiatric condition.

By comparison, 90/102 patients had no prior history of a diagnosed psychiatric condition. Largely comprising mood swings, 27 of these 90 patients reported experiencing one or more psychological symptoms in 62/646 months of treatment (10.1%). Ten of 90 (11.1%) patients without a prior history of a psychiatric condition self-reported depression during treatment. Of these 10 patients, 9 reported depression for a single month during treatment and one for two months. Therefore, the incidence of self-reported depression for patients with no prior psychiatric history was 11/646 (1.70%) months of treatment.

Statistical analysis suggested that the incidence of all psychological symptoms for patients with and without a prior history of a psychiatric condition in our study was the same (P value = 0.1246). Patients with a previous psychiatric history reported 1 month of depression of 83 (1.20%) total months of treatment. Patients without a prior psychiatric history reported symptoms in 11/646 (1.70%) total months of treatment. The incidence of depressive symptoms between the two groups was statistically the same (P value = 0.7371).

Physical Symptoms

Physical adverse effects were commonly reported during most patient-months of therapy. The four most commonly reported findings were: dry lips – 689 of 731 (94.25%), dry skin – 528 of 732 (72.13%), dry/bloodshot eyes – 215 of 729 (29.49%), and muscle aches/pains – 168 of 729 (23.05%). A rash was reported in 78 of 728 (10.71%) responses. Severe sun sensitivity/sunburn (15.66%) and nose bleeds (15.64%) were slightly more common with 114 positive responses of 728 and 729 responses respectively. Trouble with night vision occurred infrequently, with 18 of 729 (2.47%) responses. Paronychia, reported as ingrown toe/fingernails, and frequent headaches were each reported in 71 of 729 (9.74%) responses.

Patients were asked to classify the four most common symptoms as mild, moderate, or severe. Muscle aches/pains had 168 positive responses: 116 were mild (15.91%), 41

moderate (5.62%), and 11 severe (1.51%). Dry/bloodshot eyes had 215 positive responses: 159 were mild (21.81%), 49 moderate (5.62%), and 7 severe (0.96%). Dry skin had 528 positive responses: 339 were mild (46.31%), 154 moderate (21.04%), and 35 severe (4.78%). Nearly all reported dry lips, with 689 positive responses: 284 were mild (38.85%), 301 moderate (41.18%), and 104 severe (14.23%). These data are summarized in Table IV.

Comparison of Symptom Incidence by Age Group

The sample of patients was divided into two age groups, ages 11 – 15 years, representing the younger pediatric population and ages 16 – 21 years, the older adolescents. Symptom incidence was compared between the two populations (Table V). The incidence of psychological symptoms in both age groups was statistically the same. In particular, 1.59% of patients in the 11 – 15 age group reported experiencing depression compared to 1.70% of patients in the 16 – 21 age group. This difference is not statistically significant (P value = 0.905). For mood swings, 9.38% of patients in the 16 – 21 age group reported symptoms, compared to only 6.37% of patients in the 11 – 15 age group. The difference in incidence is of questionable significance (P value = 0.130), suggesting that younger pediatric acne patients are not more susceptible to mood swings while on isotretinoin.

The data indicate a similar incidence of almost all physical symptoms, regardless of age group. There was no difference in incidence between the two groups with respect to severe sun sensitivity/sunburn, rash, frequent headaches, and paronychia (P value > 0.10). There was also no difference in the incidence of dry lips and muscle aches/pains (P value > 0.08), suggesting that younger pediatric patients can expect similar symptoms to their older counterparts. Only dry/bloodshot eyes, trouble with night vision, and nose bleeds showed a statistically different incidence (P values between 0.002 and 0.026). Patients in the 16 – 21 age group reported a higher incidence for these three symptoms.

Discussion

We found that the ISS was utilized in 98.95% of isotretinoin visits and 95.0% of these surveys recorded a complete data set. We included both complete and incomplete surveys, because we felt that responses should not be invalidated simply because the patient failed to circle a response to one question on the survey. Calculations reflect only the reported data, without modification for answers omitted by the patient.

The ISS presents individualized patient-reported information, providing a long-term perspective over each treatment course. Reviewing the symptom survey with the patient at each monthly appointment permits the treating physician to closely monitor the incidence and severity of various physical and psychological symptoms and to modify treatment accordingly. Previous studies have used extensive screening criteria such as the Beck Depression Inventory²¹ or a ten-centimeter line²⁵ of severity of physical symptoms to establish the incidence of adverse events. These provide pertinent information, but may be impractical for use as a widespread screening tool. Our survey, in contrast, can be easily implemented in an outpatient clinical setting, and effectively completed by the patient or family at the beginning of their appointment. Although the simplified format does not have the thoroughness of the Beck Depression Inventory or similar depression surveys, we

believe the ISS is a useful screening tool. Importantly, our incidence results were comparable to those reported in previous studies with more intricate collection methods.

In a practice setting, the ISS allowed the patient to self-report feelings of depression, suicidal ideation, or mood swings. Prescribing physicians discussed the survey responses with the patient to assess the severity of symptoms affirmatively reported. We found that psychological symptoms were reported rarely. Using the ISS, patients experiencing depression or mood swings were quickly identified and monitored closely with follow-up questioning and medication adjustment or psychologic consultation if necessary. The documentation of individual psychological symptoms monthly using the ISS showed that these reports were generally transient, often resolving without a change in isotretinoin dose.

A small number of patients had a prior history of a diagnosed psychiatric condition. The data indicate that these patients were not at a higher risk for experiencing psychologic symptoms while on isotretinoin. This suggests that a patient's previous psychiatric history may not necessarily be a contraindication to isotretinoin treatment.

Few published studies provide individual symptom incidences from which to draw a comparison. At the time of this publication, studies investigating the incidence of mood swings were not available for comparison. Hull and Demkiw-Bartel's²⁶ prospective study reported that 4% of patients noted depressive symptoms while undergoing a 4-month treatment course of isotretinoin. An earlier prospective study by Bruno, et al.²⁷ reported the incidence of depression to be 11%. Our results for patient-reported depressive symptoms were similar, with 10.78% of patients self-reporting symptoms of depression for one or two months during treatment. The number of patients reporting depression in our study could be inflated, considering that symptoms were self-reported, and that patients undergoing isotretinoin treatment may be hyper-vigilant to possible depressive symptoms because of prescribing physician and black-box medication warnings.

In spite of the potential for over-reporting of depression on self-completed surveys, patients only reported depressive symptoms on 12/729 monthly surveys (1.65%). This finding is reassuring that depressive symptoms, if related to isotretinoin treatment, are potentially temporary in duration. Patients also tended to report depressive symptoms later in their course of treatment with the average onset at approximately 14 weeks into treatment. This result is similar to that reported by Scheinman, et al.²⁸ who found the average duration of therapy prior to onset of depression to be 14 weeks.

The incidence rate and severity assessment of physical symptoms reported by McLane²⁶ closely resemble the results of our study. McLane utilized a 10-cm line on which patients subjectively denoted the severity of their symptoms, whereas our symptom survey asked the patients to choose between 'mild/moderate/severe' categories. Despite the differences between these two approaches, McLane reported comparable findings for the more common physical symptoms. The ISS is brief with both psychological and physical symptoms listed on one page. Ease of completion should not be underestimated for a screening tool that aims to provide optimal results with monthly patient compliance.

A comparison of adverse effects of isotretinoin between younger pediatric and older adolescent patients showed that younger pediatric patients (age 11 – 15) are not more susceptible to symptoms than older adolescents (age 16 – 21). Three symptoms (nose bleeds, dry/bloodshot eyes, and trouble with night vision) showed statistically significant higher reported values in the young adult population. The higher reported values for trouble with night vision may reflect a reporting bias, because this population is of driving age and active at night, making them more likely to notice and report this symptom.

This study shows that a monthly patient-completed ISS provides a useful method for standardized screening of isotretinoin-induced symptoms. Overall, pediatric patients tolerated isotretinoin treatment well, and concerns that younger patients may have an increased risk of side effects were not confirmed. The ISS can help to manage young pediatric patients safely on isotretinoin if the severity of their acne warrants early intervention. Our data indicate that a prior psychiatric history may not necessarily preclude treatment with isotretinoin although the sample size was small. A study of this sub-population, with greater power, is an area of future interest.

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References

1. Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. *Pediatrics*. 2006; 118:1188–99. [PubMed: 16951015]
2. Farrell LN, Strauss JS, Stranieri AM. The treatment of severe cystic acne with 13-cis-retinoic acid: evaluation of sebum production and the clinical response in a multiple-dose trial. *J Am Acad Dermatol*. 1980; 3:602–11. [PubMed: 6451637]
3. Leyden JJ. The role of isotretinoin in the treatment of acne: personal observations. *J Am Acad Dermatol*. 1998; 39:S45–9. [PubMed: 9703123]
4. Nguyen EH, Wolverton SE. Systemic retinoids. *Comprehensive dermatologic drug therapy*. 2001:269–310.
5. Charakida A, Mouser PE, Chu AC. Safety and side effects of the acne drug, oral isotretinoin. *Expert Opin Drug Saf*. 2004; 3:119–29. [PubMed: 15006718]
6. Tom WL, Barrio VR. New insights into adolescent acne. *Curr Opin Pediatr*. 2008; 20:436–40. [PubMed: 18622200]
7. Goulden V. Guidelines for the management of acne vulgaris in adolescents. *Paediatr Drugs*. 2003; 5:301–13. [PubMed: 12716217]
8. Strahan JE, Raimer S. Isotretinoin and the controversy of psychiatric adverse effects. *Int J Dermatol*. 2006; 45:789–99. [PubMed: 16863513]
9. 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. [PubMed: 7777014]
10. Ellis CN, Krach KJ. Uses and complications of isotretinoin therapy. *J Am Acad Dermatol*. 2001; 45:S150–7. [PubMed: 11606947]
11. O'Donnell J. Overview of existing research and information linking isotretinoin (accutane), depression, psychosis, and suicide. *Am J Ther*. 2003; 10:148–59. [PubMed: 12629595]
12. Hull PR, D'Arcy C. Isotretinoin use and subsequent depression and suicide: presenting the evidence. *Am J Clin Dermatol*. 2003; 4:493–505. [PubMed: 12814338]
13. Magin P, Pond D, Smith W. Isotretinoin, depression and suicide: a review of the evidence. *Br J Gen Pract*. 2005; 55:134–8. [PubMed: 15720936]

14. Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. *Semin Cutan Med Surg.* 2005; 24:92–102. [PubMed: 16092797]
15. Jick SS, Dremers HM, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide, and attempted suicide. *Arch Dermatol.* 2000; 136:1231–6. [PubMed: 11030769]
16. Azoulay L, Blais L, Koren G, LeLorier J, Bérard A. Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. *J Clin Psychiatry.* 2008; 69:526–32. [PubMed: 18363422]
17. Brasi JR. Monitoring people treated with isotretinoin for depression. *Psychol Rep.* 2007; 100:1312–4. [PubMed: 17886520]
18. Kaymak Y, Kalay M, Ilter N, Taner E. Incidence of depression related to isotretinoin treatment in 100 acne vulgaris patients. *Psychol Rep.* 2006; 99:897–906. [PubMed: 17305209]
19. Ferahbas A, Turan MT, Esel E, Utas S, Lutlugun C, Kilic CG. A pilot study evaluating anxiety and depressive scores in acne patients treated with isotretinoin. *J Dermatolog Treat.* 2004; 15:153–7. [PubMed: 15204147]
20. Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol.* 2001; 45:515–9. [PubMed: 11568740]
21. Ng CH, Tam MM, Celi E, Tate B, Schweitzer I. Prospective study of depressive symptoms and quality of life in acne vulgaris patients treated with isotretinoin compared to antibiotic and topical therapy. *Australas J Dermatol.* 2002; 43:262–8. [PubMed: 12423432]
22. Chia CY, Lane W, Chibnall J, Allen A, Siegfried E. Isotretinoin therapy and mood changes in adolescents with moderate to severe acne: a cohort study. *Arch Dermatol.* 2005; 141:557–60. [PubMed: 15897376]
23. Hull PR, D'Arcy C. Acne, depression, and suicide. *Dermatol Clin.* 2005; 23:665–74. [PubMed: 16112443]
24. Yan AC. Current concepts in acne management. *Adolesc Med Clin.* 2006; 17:613–37. abstract x-xi. [PubMed: 17030282]
25. McLane J. Analysis of common side effects of isotretinoin. *J Am Acad Dermatol.* 2001; 45:S188–94. [PubMed: 11606952]
26. Hull PR, Demkiw-Bartel C. Isotretinoin use in acne: prospective evaluation of adverse events. *J Cutan Med Surg.* 2000; 4:66–70. [PubMed: 11179927]
27. Bruno NP, Beacham BE, Burnett JW. Adverse effects of isotretinoin therapy. *Cutis.* 1984; 33:484–6. 489. [PubMed: 6236956]
28. Scheinman PL, Peck GL, Rubinow DR, DiGiovanna JJ, Abangan DL, Ravin PD. Acute depression from isotretinoin. *J Am Acad Dermatol.* 1990; 22:1112–4. [PubMed: 2142496]

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DERMATOLOGY
Isotretinoin Symptom Survey
Return Patient

DTF333
DTF333

PATIENT INFORMATION

Please identify by circling any of the following symptoms if you have experienced them since your last visit with the doctor.

Dry Lips:	no / mild / moderate / severe
Dry or Blood Shot Eyes:	no / mild / moderate / severe
Dry Skin:	no / mild / moderate / severe
Muscle Aches or Pains:	no / mild / moderate / severe
Nose Bleeds:	no / yes
Frequent Headaches:	no / yes
Mood Swings:	no / yes
Depression:	no / yes
Suicidal Thoughts:	no / yes
Ingrown Toenails/Fingernails:	no / yes
Rash:	no / yes
Trouble with Night Vision:	no / yes
Severe Sun Sensitivity or Sunburn:	no / yes

Reviewed: _____ (MD Signature) Date: _____

(Lawrence Eichenfield, MD / Shaila Friedlander, MD / Magdalena Dahl, MD / Victoria R. Berris, MD / Neil Giblin, MD / Lisa Clayton, PA)

Accutane Symptom Survey (Rev 03/01/06)

Figure 1.

Figure 2.
Incidence of Adverse Effects Over 760 Months of Isotretinoin Treatment

Table I

Completion of “Isotretinoin Symptom Survey”

Survey Status	No. of Surveys	%
Months Complete	722	95.00%
Months Incomplete	30	3.95%
Months Missing	8	1.05%

Table II

Incidence of Adverse Effects

Adverse Effect	No. of Completed Surveys	Months Reporting Effect	%	P Value [*]
Dry Lips	731	689	94.25%	<0.001
Dry Skin	732	528	72.13%	<0.001
Dry/Bloodshot Eyes	729	215	29.49%	<0.001
Muscle Aches/Pains	729	168	23.05%	<0.001
Severe Sun Sensitivity/Sunburn	728	114	15.66%	<0.001
Nose Bleeds	729	114	15.64%	<0.001
Rash	728	78	10.71%	<0.001
Paronychia	729	71	9.74%	<0.001
Frequent Headaches	729	71	9.74%	<0.001
Mood Swings	729	57	7.82%	<0.001
Trouble with Night Vision	729	18	2.47%	<0.001
Depression	729	12	1.65%	<0.001
Suicidal Thoughts	729	0	0.00%	1.0000

* P values test whether “%” is statistically greater than zero.

Table III

95% Confidence Intervals for Adverse Effect Incidence

Adverse Effect	Lower Bound	Upper Bound
Dry Lips	92.57%	95.94%
Dry Skin	68.88%	75.38%
Dry/Bloodshot Eyes	26.18%	32.80%
Muscle Aches/Pains	19.99%	26.10%
Severe Sun Sensitivity/Sunburn	13.02%	18.30%
Nose Bleeds	13.00%	18.27%
Rash	8.47%	12.96%
Paronychia	7.59%	11.89%
Frequent Headaches	7.59%	11.89%
Mood Swings	5.87%	9.77%
Trouble with Night Vision	1.34%	3.60%
Depression	0.72%	2.57%
Suicidal Thoughts	0.00%	0.00%

Table IV

Severity of Most Common Adverse Effects

Adverse Effect	No. of Completed Surveys	Months Reporting the Effect	%	P Value*
Muscle Aches/Pains	729			
Mild		116	15.91%	<0.001
Moderate		41	5.62%	<0.001
Severe		11	1.51%	<0.001
Dry Lips	731			
Mild		284	38.85%	<0.0001
Moderate		301	41.18%	<0.0001
Severe		104	14.23%	<0.0001
Dry Skin	732			
Mild		339	46.31%	<0.0001
Moderate		154	21.04%	<0.0001
Severe		35	4.78%	<0.0001
Dry/Bloodshot Eyes	729			
Mild		159	21.81%	<0.0001
Moderate		49	6.72%	<0.0001
Severe		7	0.96%	0.0039

* P values test whether “%” is statistically greater than zero.

Table V

Comparison of Adverse Effect Incidence by Age Group

Adverse Effect	Age 11 – 15				Age 16 – 21			
	No. of Completed Surveys	Months Reporting Symptom	%	P Value *	No. of Completed Surveys	Months Reporting Symptom	%	P Value **
Dry Lips	379	352	92.88%	<0.0001	352	337	95.74%	<0.0001
Dry Skin	379	262	69.13%	<0.0001	353	266	75.35%	<0.0001
Dry/Bloodshot Eyes	377	97	25.73%	<0.0001	352	118	33.52%	<0.0001
Muscle Aches/Pains	377	77	20.42%	<0.0001	352	91	25.85%	<0.0001
Severe Sun Sensitivity/Sunburn	377	64	16.98%	<0.0001	351	50	14.25%	<0.0001
Nose Bleeds	377	48	12.73%	<0.0001	352	66	18.75%	<0.0001
Rash	378	47	12.43%	<0.0001	350	31	8.86%	<0.0001
Paronychia	377	39	10.34%	<0.0001	352	32	9.09%	<0.0001
Frequent Headaches	377	36	9.55%	<0.0001	352	35	9.94%	<0.0001
Mood Swings	377	24	6.37%	<0.0001	352	33	9.38%	<0.0001
Depression	377	6	1.59%	0.006770	352	6	1.70%	0.006744
Trouble with Night Vision	377	3	0.80%	0.041019	352	15	4.26%	<0.0001
Suicidal Thoughts	377	0	0.00%	1.0000	352	0	0.00%	1.0000

* Tests whether “%” is statistically greater than zero

** Tests whether “%” is statistically different between “Age 11 – 15” and “Age 16 – 21”