Oral Nicotinamide Reduces Actinic Keratoses in Adults with Sun-Damaged Skin

Stacy E. Legg
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Abstract

Background: Actinic keratoses (AKs) are skin lesions primarily caused by ultraviolet (UV) exposure. They are precancerous lesions and can develop into non-melanoma skin cancer. Exposure to UV radiation leads to the development of AKs by several mechanisms. UV radiation damages cellular DNA, depletes cellular energy levels, and suppresses the immune system. Nicotinamide is a form of vitamin B3. Topical nicotinamide increases cellular energy levels and protects against immunosuppression in humans. The question arises, could oral nicotinamide mitigate the harmful effects of UV radiation, and be useful in the reduction of AKs?

Methods: An exhaustive literature search was conducted using MEDLINE - Ovid, Web of Science, and Google Scholar. The search terms nicotinamide and actinic keratosis were used. Applicable articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

Results: Two studies met eligibility criteria and were included. Both were randomized, controlled, double-blinded trials. One trial included two cohorts, with different doses of nicotinamide used. Cohort 1 found that the number of AKs were 35% less in the nicotinamide group at 2 months (95% confidence interval (CI): 23-45%; p

Conclusion: The two studies reviewed demonstrated a reduction in AKs in patients taking oral nicotinamide. Providers should consider oral nicotinamide supplementation in patients with sun-damaged skin. Further research is needed to explore the action of nicotinamide on the prevention of AKs and NMSC.

Keywords: Nicotinamide and actinic keratoses

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A Clinical Graduate Project Submitted to the Faculty of the

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Faculty Advisor: Jennifer Van Atta, PA-C, MS

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Stacy E. Legg received her BA in Psychology from Whitman College. Before PA school, she held several research positions at Oregon Health & Science University. She was involved in basic science research in Behavioral Neuroscience focusing on addiction. Transitioning to clinical research in Endocrinology sparked her interest in patient care. She worked on research studies concerning the pituitary and hormone deficiencies. Stacy has called Portland, OR home for over 20 years, and plans to remain in the Pacific Northwest after graduating. In her free time she enjoys hiking, biking, and skiing.
Abstract

**Background:** Actinic keratoses (AKs) are skin lesions primarily caused by ultraviolet (UV) exposure. They are precancerous lesions and can develop into non-melanoma skin cancer. Exposure to UV radiation leads to the development of AKs by several mechanisms. UV radiation damages cellular DNA, depletes cellular energy levels, and suppresses the immune system. Nicotinamide is a form of vitamin B3. Topical nicotinamide increases cellular energy levels and protects against immunosuppression in humans. The question arises, could oral nicotinamide mitigate the harmful effects of UV radiation, and be useful in the reduction of AKs?

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**Results:** Two studies met eligibility criteria and were included. Both were randomized, controlled, double-blinded trials. One trial included two cohorts, with different doses of nicotinamide used. Cohort 1 found that the number of AKs were 35% less in the nicotinamide group at 2 months (95% confidence interval (CI): 23-45%; p<0.0001) and at 4 months (95% confidence interval (CI): 18-48%; p=0.0006). Cohort 2 found that the number of AKs were 15% less in the nicotinamide group at 2 months (95% confidence interval (CI): 0-28%; p=0.046) and 29% less at 6 months (95% confidence interval (CI): 11-44%; p=0.005). In the second study, the number of AKs were 11% lower in the nicotinamide group at 3 months (p=0.01), 14% lower at 6 months (p<0.001), 20% lower at 9 months (p<0.001), and 13% lower at 12 months (p=0.001).

**Conclusion:** The two studies reviewed demonstrated a reduction in AKs in patients taking oral nicotinamide. Providers should consider oral nicotinamide supplementation in patients with sun-damaged skin. Further research is needed to explore the action of nicotinamide on the prevention of AKs and NMSC.

**Keywords:** Nicotinamide and actinic keratoses
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Table I: Characteristics of Reviewed Studies
Table II: Summary of Finding

List of Abbreviations

AE Adverse event
AKs Actinic keratoses
BCC Basal cell carcinoma
NMSC Non-melanoma skin cancer
SCC Squamous cell carcinoma
UV Ultraviolet
Oral Nicotinamide Reduces Actinic Keratoses in Adults with Sun-Damaged Skin

BACKGROUND

Actinic keratoses (AKs) are skin lesions primarily caused by ultraviolet (UV) exposure. They are classified as dysplastic keratiocytic lesions and can have assorted presentations, but often appear as plaques or papules on an erythematous base. Actinic keratoses develop most commonly on chronically sun-exposed areas such as the scalp, face, neck, and upper extremity. They are precancerous lesions and can develop into non-melanoma skin cancer (NMSC), most likely squamous cell carcinoma (SCC). Non-melanoma skin cancer is the most commonly diagnosed cancer in the United States, and the incidence is increasing.

Primary prevention of NMSC includes wearing protective clothing, using sunscreen, and sun avoidance. More specifically, using sunscreen can help reduce the number of AKs and prevent SCC. The rate of sunscreen use among adults is low. Only 18.1% of men and 42.6% of women report regular use of sunscreen on the face. Both men and women reported even less sunscreen use on other commonly sun-exposed skin. With the continuing increase in skin cancer, and the non-adherence to current preventative measures, there needs to be additional tools for the prevention of these diseases.

Exposure to UV radiation leads to the development of AKs by several mechanisms. UV radiation damages cellular DNA, resulting in genetic mutation and the expression of abnormal cells. UV radiation also depletes cellular ATP levels. With low energy levels, a cell cannot repair damage. Finally, UV radiation suppresses the immune system by altering the function of antigen presenting cells, T-cells, natural killer cells and cytokine function. Organ transplant patients, who are on chronic immunosuppressant drugs, are significantly more likely to develop AKs and skin cancers.
Nicotinamide is an amide of vitamin B3 and has been used in the treatment of various skin conditions such as acne vulgaris.\textsuperscript{9} Nicotinamide is safe and well tolerated. Unlike niacin, nicotinamide lacks the vasodilatory effects that cause flushing and hypotension.\textsuperscript{10} Nicotinamide is a precursor of NAD\textsuperscript{+} and is needed for ATP production. Sivapirabu et al\textsuperscript{11} found topical nicotinamide to increase cellular energy levels and protect against immunosuppression in humans. The question arises, could oral nicotinamide mitigate the harmful effects of UV radiation, and be useful in the reduction of AKs? Specifically, does oral nicotinamide reduce actinic keratoses in adults with sun-damaged skin?

**METHODS**

An exhaustive literature search was conducted using the following search engines: MEDLINE - Ovid, Web of Science, and Google Scholar. The search terms nicotinamide and actinic keratosis were used. Inclusion criteria required human studies and studies in the English language. Trials that used a topical application of nicotinamide were excluded. Applicable articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).\textsuperscript{12}

**RESULTS**

The initial literature search resulted in 8 articles. Screening using the eligibility criteria narrowed the results to 2 articles.\textsuperscript{13,14} Both articles were randomized controlled clinical trials.

**Surjana et al**

This study\textsuperscript{13} was published in 2012 and was a randomized, controlled, double-blinded trial. The authors were interested if oral nicotinamide could reduce the number of AKs in participants with UV damaged skin. This article consisted of two separate cohorts. Cohort 1 was
conducted from June-October 2009. Groups received 500 mg of nicotinamide twice daily or a matched placebo. Cohort 2 was conducted from August-November 2010. Groups received either 500 mg of nicotinamide once daily or a matched placebo. The primary endpoint of both cohorts was the number of AKs at 4 months. The secondary endpoint was the number of new skin cancers (BCC and SCC) developed during the 4-month study.\textsuperscript{13}

Participants were recruited from the Royal Prince Hospital Dermatology Clinics in Sydney, Australia. Included participants had a minimum of 4 palpable AKs in the treatment areas (face, scalp, and upper extremities) and were required to be healthy and immune-competent. The authors did not elaborate on the eligibility criteria any further in the published article. The Australian New Zealand Clinical Trials Registry\textsuperscript{15} was queried for additional information. Men and women 18 years or older were eligible to participate. Exclusion criteria were pregnancy or breastfeeding, the use of immunosuppressive or photosensitizing agents, nicotinamide or other vitamin supplement use, dermatitis in the treatment areas, liver disease, or carbamazepine use. After meeting criteria, 35 participants were randomized into cohort 1 and 41 participants were randomized into cohort 2.\textsuperscript{13}

The treatment allocation sequence was computer generated by an author using a permuted block method with a block size of six. Randomization occurred in a 1:1 ratio to receive either 500 mg of nicotinamide (Nature’s Own) or a matched placebo (Australian Custom Pharmaceuticals). Participants remained blinded to their treatment allocation throughout the study. Before randomization, participants underwent a complete skin check, and were advised to wear sunscreen daily during the trial. Any unused drug was returned at the visits to be counted and recorded for compliance.\textsuperscript{13}

A blinded author identified the AKs by palpation and observation at the baseline, the 2-
month visits, and the 4-month visits. The authors analyzed the data under the intention to treat principle. The AK data was skewed to the right, and required a natural log transformation. Using an analysis of covariance adjusting for baseline AK number, the relative difference between the groups was calculated. Cohort 1 found that the number of AKs were 35% less in the nicotinamide group at 2 months (95% confidence interval (CI): 23-45%; p<0.0001) and at 4 months (95% confidence interval (CI): 18-48%; p=0.0006). Cohort 2 found that the number of AKs were 15% less in the nicotinamide group at 2 months (95% confidence interval (CI): 0-28%; p=0.046) and 29% less at 6 months (95% confidence interval (CI): 11-44%; p=0.005). Compliance in taking the tablets was calculated at 94-98% for both cohorts. One patient experienced an adverse event (AE), which was nausea while concomitantly taking aspirin.\textsuperscript{13}

The investigators concluded that nicotinamide is effective at reducing the number of AKs in participants compared to placebo. Limitations of the study included the short duration and small sample size. The first author did the AK assessments and new AKs were not confirmed histologically. Sunscreen use was encouraged, but compliance not tracked.

\textbf{Chen et al}

This study\textsuperscript{14} was published in 2015 and was a randomized, controlled, double-blinded trial. The authors were interested if oral nicotinamide could reduce the number of new NMSCs and AKs in patients with UV damaged skin. Treatment was either 500 mg of nicotinamide twice daily or a matched placebo for 12 months (both provided by Insolar, Blackmores). The primary endpoint was the number of new, confirmed NMSCs. The secondary endpoint included the number of new BCCs, SCCs, and AKs, and the safety profile of nicotinamide. The authors also looked at oral nicotinamide’s effect on and cognitive functioning and epidermal water loss.\textsuperscript{14}

Men and women 18 years or older with at least 2 NMSCs in the last 5 years were
recruited from 2 hospitals in Sydney, Australia (Royal Prince Alfred and Westmead). Exclusion criteria were immunosuppression, pregnancy or breastfeeding, impaired liver or kidney function, active peptic ulcer disease, recent MI, and hypotension. Genetic skin cancer syndromes, a large area of skin cancer, and use of nicotinamide, oral retinoids, or other treatment for AK in the last 4 weeks was also exclusionary. Participants with a history of metastatic cancer, invasive melanoma, or an internal malignancy in the last 5 years were also excluded. After meeting criteria, 386 participants were randomized. Daily sunscreen use was instructed. Unused drug was returned at each visit to be counted and recorded for compliance.14

Randomization was done centrally in a 1:1 ratio with stratification according to a 5-year history of NMSC (≤ 6 or >6 lesions), sex and study site. A blinded author at each site identified the AKs by palpation and observation at the baseline, at 3-month intervals. Treatment areas consisted of the face, scalp, forearms, and hands. A blinded histopathologist confirmed new lesions. The authors analyzed the data under the intention to treat principle using a mixed-effects model for repeated measures. The repeated measures included study group, center, baseline value, time point, and interaction between time and study group. The number of AKs was 11% lower in the nicotinamide group at 3 months (p=0.01), 14% lower at 6 months (p<0.001), 20% lower at 9 months (p<0.001), and 13% lower at 12 months (p=0.001). The median rate of compliance with treatment over the 12 months was 96% in the nicotinamide group and 94% in the placebo group. Rate of sunscreen use was higher in the placebo group than the nicotinamide group throughout the study, with significant differences at 6 months (58% vs 47% p=0.02) and 9 months (59% vs 48% p=0.03). No significant differences in AEs was found between the two groups.14

Investigators concluded that nicotinamide is effective at reducing the number of AKs in
patients compared to placebo. A limitation to the study is that two authors did the AK assessments, and there is no test for inter-rater reliability.

**DISCUSSION**

The two studies\textsuperscript{13, 14} reviewed demonstrated a reduction in AKs in patients taking oral nicotinamide compared to placebo. The magnitude of the reduction was noticeably greater in the Surjana et al study.\textsuperscript{13} Both studies found nicotinamide to be well tolerated and safe. Both studies monitored blood counts, renal and kidney function, with no significant changes found between the treatment or placebo group.

In analyzing the current evidence, there are some limitations that need to be addressed. Both studies were conducted by a similar group of investigators in Sydney, Australia. Three of the five authors from the Surjana et al study\textsuperscript{13} were represented in the Chen et al study.\textsuperscript{14} The body of research about this clinical question is quite limited; these are the only two currently published clinical trials. This raises the possibility of publication bias.

As for detection of the primary outcome, palpation and observation is often used to diagnose AKs. A biopsy is preformed if the diagnosis is unclear or to rule out NMSC. AKs can have many presentations leading to difficulty in diagnosis. Weinstock et al\textsuperscript{16} found AK counts varied widely between dermatologists when looking at a single participant. Counting AKs was deemed an unreliable approach. Both studies reviewed here used palpation and observation as the primary method of assessing AKs. The Chen et al study\textsuperscript{14} histologically confirmed any new AKs, but had different authors at each site completing the AK counts, potentially introducing bias. Both studies acknowledged sunscreen use as a prognostic factor in the reduction of AKs. The Surjana et al study\textsuperscript{13} encouraged participants to use sunscreen daily, but did not track compliance.
In the Surjana et al study,\textsuperscript{13} the sample size was quite small, and the participants had a large variation in the number of AKs at baseline, resulting in skewed data and large confidence intervals. The duration of the study was also quite short. In the Chen et al study,\textsuperscript{14} the confidence intervals were also quite wide. The inclusion criteria for this study focused on NMSC, not AKs. The range of AKs at baseline was 0-205 for the nicotinamide group and 0-214 for the placebo group, likely contributing to the lack of precision.

The development of new NMSC was also explored as an endpoint in these studies. Chen et al\textsuperscript{14} found the rate of new NMSC was significantly lower at 12 months with nicotinamide than with placebo (relative difference=23%, \( p=0.02 \)). This suggests nicotinamide may have a broader application in preventing new NMSC and in chemoprevention, but further research is needed to explore this topic.

CONCLUSION

Actinic keratoses are precancerous lesions that can progress to NMSC. The incidence of skin cancer is increasing, and current preventative measures show low compliance. The research reviewed found oral nicotinamide reduced the number of AKs versus placebo in participants with UV damaged skin. Providers should consider oral nicotinamide supplementation in this subset of patients due to its safety and likely efficacy. Further research is needed to explore the action of nicotinamide on the prevention of AKs and NMSC.

References


## Table I. Characteristics of Reviewed Studies

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<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Inconsistency</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Upgrade Criteria</th>
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<td>RCT</td>
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<td>Serious\textsuperscript{b}</td>
<td>Likely\textsuperscript{c}</td>
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<tr>
<td>Chen et al\textsuperscript{14}</td>
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<td>Not Serious</td>
<td>Not Serious</td>
<td>Serious\textsuperscript{d}</td>
<td>Likely\textsuperscript{e}</td>
<td>None</td>
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\textsuperscript{a}Didn’t confirm AKs histopathologically. Not all prognostic factors tracked.
\textsuperscript{b}Small sample size and wide confidence intervals.
\textsuperscript{c}Limited research. Crossover of authors in both RCTs.
\textsuperscript{d}Wide confidence intervals.
## Table II. Summary of Findings

### Study 1

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<td>18</td>
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### Study 2

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<tr>
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<td>46.3 (26.5)</td>
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<td>30.6 (16.3)</td>
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### Chen et al

<table>
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