feine intake only at baseline as well as updated intake at individual cycles in secondary analyses.

Cox proportional hazards regression models were used to estimate relative risks (RRs) and 95% CIs. Analyses were updated because the main exposure, outcome, and covariates were all time varying. We had multivariate models with or without smoking. Analyses were conducted using SAS software, version 9.2 (SAS Institute Inc). The study was approved by the institutional review board of Brigham and Women’s Hospital. Our receipt of each completed questionnaire implied participant’s informed consent of the present study.

Results. A total of 82,539 participants were included. The baseline characteristics of participants by intake of caffeine (in quintiles) are listed in Table 1. Participants with higher consumption of caffeine were more likely to be current smokers and had a higher quantity of alcohol intake.

During 1,140,758 person-years of follow-up, we identified 986 incident cases of psoriasis. Risk of psoriasis was moderately elevated with increasing coffee consumption in the age-adjusted model. However, this trend became nonsignificant after adjustment for smoking. We also evaluated the association between decaffeinated coffee and risk of psoriasis, which was not significant. A trend toward increased risk of psoriasis was observed with higher caffeine intake in the age-adjusted model. The association became null after adjustment for smoking (Table 2).

Stratified analyses did not show significant findings among nonsmokers. Secondary analysis by only using different measures of coffee and caffeine consumption did not reveal material change of the effect estimation (eTable 1 and eTable 2; available at http://www.archdermatol.com).

Comment. In this prospective cohort study, we did not observe a material change of psoriasis incidence associated with coffee or caffeine intake, after adjusting for known confounders. Smoking appears to be the major confounder underlying the observed significant association between coffee and caffeine intake and risk of psoriasis in age-adjusted models. Consistent with published case-control studies, present data did not lend support to the effect of coffee or caffeine intake on risk of psoriasis. Our study had retrospective characteristics, given that information on psoriasis was collected in 2005, and misclassification is possible. Further studies are warranted to confirm our findings.

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Comparison of Refined and Crude Indigo Naturalis Ointment in Treating Psoriasis: Randomized, Observer-Blind, Controlled, Intrapatient Trial

Our group’s previous studies have shown that topical application of indigo naturalis significantly improves psoriatic symptoms. However, patient compliance is hindered because the preparation is unsightly and stains clothing.

To improve patient compliance, we have developed a refined formulation in which the blue dye component is removed, leaving only a purple-red color that is closer to natural skin tones and less prone to stain clothing. Herein, we describe a study of the efficacy and safety of this new product.
Methods. The refined indigo naturalis ointment was prepared for our study by mixing indigo naturalis powder with olive oil, filtering, and then mixing with petroleum jelly and wax. The crude form was prepared as described previously.1 The concentrations of indirubin, previously identified as the main active ingredient in indigo naturalis, were found to be 0.105 mg/g and 0.138 mg/g for the refined and crude ointments, respectively.

After institutional review board approval, we recruited patients from November 2009 to May 2010 using the criteria listed in the Table. At baseline, data on the duration of psoriasis, total body surface area involvement (BSA), and Psoriasis Area Severity Index (PASI) were collected. Two symmetrically comparable plaques on each patient were identified, one randomly assigned to receive refined ointment, and the other assigned to receive crude ointment. Patients were

Table. Inclusion and Exclusion Criteria

<table>
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<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>1. Diagnosis of plaque psoriasis based on clinical assessment by 2 dermatologists at least 1 year prior to entry into the study</td>
<td>1. Nonplaque (ie, pustular, guttate, or erythrodermic) or drug-induced forms of psoriasis</td>
</tr>
<tr>
<td>2. Mild to moderate plaque psoriasis with bilateral symmetric lesions</td>
<td>2. Total body surface area involvement more than 60%</td>
</tr>
<tr>
<td>3. Age between 20 and 65 years</td>
<td>3. History of allergy to indigo naturalis</td>
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<tr>
<td>4. Good general health as evidenced by results of blood tests and assays of renal and liver function conducted prior to commencing the study</td>
<td>4. Systemic therapy within 4 weeks before enrollment, phototherapy within 3 weeks, or use of topical psoriasis agents within 2 weeks before enrollment</td>
</tr>
<tr>
<td>5. Agreement to avoid pregnancy for the duration of the study</td>
<td>5. Use of medications that affect psoriasis during the study or unwillingness to comply with study protocol</td>
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Figure 1. Mean Psoriasis Severity Index (PSI) (A), clearing percentage (B), and improvement in lesions (C and D) treated with refined and crude indigo naturalis ointment. A, The PSI score (0-12). B, Clearing percentage of target plaque. C, Improvement from baseline (percentage). All data in panels A-C are mean (SD) values measured during the 8-week treatment period. D, Lesion change at week 8 after treatment with refined or crude indigo naturalis ointment. Lesion change was classified as worse (<0% improvement), no change (0% to <25% improvement), mild improvement (≥25% to <50% improvement), moderate improvement (≥50% to <75% improvement), near clearance (≥75% to <90% improvement), or clearance (≥90% improvement). The improvement percentage of the lesion was calculated as \( \frac{[\text{Area}_{\text{baseline}} \times \text{PSI}_{\text{baseline}} - \text{Area}_{\text{follow-up visit}} \times \text{PSI}_{\text{follow-up visit}}]}{\text{Area}_{\text{baseline}} \times \text{PSI}_{\text{baseline}}} \times 100\% \).
instructed to avoid cross-contamination between the 2 treatment sites by washing their hands thoroughly between applications. Treatment was performed until complete clearing, up to a maximum period of 8 weeks, and immediately stopped if adverse events occurred that were possibly related to treatment.

After the skin was cleaned, photographs of the lesions were taken, and lesion severity was evaluated at baseline and at weeks 2, 4, 6, and 8. Efficacy was assessed by PSI, representing a composite of scaling, erythema, induration, and clearing percentage of each target plaque, with 0% representing clearance. Using a photograph from a previous study as the standard, 2 observers (Y.-H.H. and Y.-C.C.) independently rated each photograph without knowing which ointment had been used. At the end of the trial, the patients were asked which ointment they preferred.

Adverse events were recorded at each visit, and it was determined whether they were related to the study medication. Findings of blood tests and assays of liver and renal function were also evaluated.

Statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc). The paired t test and mixed-effect model were used, with significance level (alpha) set at 0.05. The trial was registered under clinicaltrials.gov Identifier: NCT01022502.

**Results.** Of 38 enrolled patients, 35 completed the study. Mean (SD) age was 42.0 (12.6) years; duration of psoriasis was 11.6 (10.7) years; PASI was 11.5 (7.9); and BSA was 18.4% (15.1%). The mean (SD) areas of lesions targeted for treatment with refined and crude ointment were 69.3 (85.2) cm² and 73.0 (85.1) cm², respectively (P = .58), while the PSIs were 9.1 (2.4) and 8.8 (2.3), respectively (P = .14). Three patients were withdrawn from the study at weeks 4, 5, and 6 owing to employment-related conflicts, severe itching, and failure to follow up, respectively.

Throughout the study, lesions treated with refined ointment and those treated with crude ointment both showed significant improvement (Figure 1A and B). For lesions treated with refined ointment, the combined PSI and lesion area score showed a 74.28% improvement (P < .001) (Figure 1C). For lesions treated with crude ointment, the improvement was 74.80% (P < .001) (Figure 1C).

Clearance or near clearance was achieved in 24 of the 35 target lesions (69%) after treatment with refined ointment, compared with 23 of the 35 target lesions (66%) treated with crude ointment (P > .65) (Figure 1D). Representative photographs illustrating the degree of improvement are shown in Figure 2.

At week 8, 31 of 35 patients reported a preference for the refined ointment; 1 patient preferred the crude ointment; and 3 had no preference.

Itching sensation was reported by 8 and 11 patients, while erythematous changes were reported by 1 and 3 patients at the lesions treated with refined and crude ointments, respectively. However, these adverse effects occurred at the beginning of treatment and resolved after a couple of days. Patch test results revealed no allergic responses, while blood tests and assays of liver and renal function showed no significant findings.

**Comment.** Our group has previously analyzed the antipsoriatic effects of indigo naturalis. The major active ingredient, indirubin, a red 3,2'-bisindole isomer, mediates the process by promoting differentiation and inhibiting proliferation of epidermal keratinocytes. We speculate that indirubin plays a similar role in the refined ointment.

Patient acceptance of indigo naturalis has been handicapped by its dark blue color, which is aesthetically problematic in exposed areas like the face, and it stains clothing. By removing the blue dye indigo and retaining the indirubin, our refining process produces...
an ointment that is less visible in exposed areas and less likely to stain clothing. From the results of this study, we conclude that this new refined formulation is not only more user friendly but has no disadvantage in efficacy or safety. This is a significant milestone in establishing indigo naturalis as a widely acceptable alternative psoriasis treatment.

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COMMENTS AND OPINIONS

Gabapentin Not Shown to Prevent Postherpetic Neuralgia

I read with interest “Prevent Rather Than Treat Postherpetic Neuralgia by Prescribing Gabapentin Earlier in Patients With Herpes Zoster,”[1] the Practice Gaps commentary accompanying “Incidence of Postherpetic Neuralgia After Combination Treatment with Gabapentin and Valacyclovir in Patients With Acute Herpes Zoster” by Lapolla et al.2 The commentary states that the study “provides convincing evidence that the use of gabapentin combined with valacyclovir during an episode of acute herpes zoster reduces the rates of PHN [postherpetic neuralgia].”[1] Further interpreting the study results, the commentary authors also recommend that dermatologists should prescribe gabapentin to prevent PHN.3

The work by Lapolla and colleagues2 was an open label pilot study assessing the incidence of PHN in subjects treated with a combination of valacyclovir and gabapentin. This study does not include a contemporaneous control group; therefore, we cannot draw conclusions about the effect of gabapentin on the development of PHN. Lapolla et al2 do compare their reported incidence of PHN with that found in historic controls described in a meta-analysis of 6 randomized controlled studies of antiviral agents used in the treatment of acute zoster.3 The use of these historic controls is problematic owing to differences in subject treatment and differences in the outcome measures used to assess pain. The use of historic controls makes it impossible to know if the observed decreased incidence in persistent pain is due to gabapentin, differences in subject treatment, or differences in responsiveness of the outcome measures chosen to assess pain.

Recommending gabapentin as an agent to prevent PHN is premature at this time. There are no data that support the use of gabapentin as a preventive agent for PHN. Furthermore, prescribing gabapentin for an indication not supported by the literature will contribute to rising healthcare costs and may cause patient harm. If all 1 million adults estimated to develop shingles this year are treated with 3600 mg/d of gabapentin for 1 month, it will cost an estimated $493,800,000. This cost is doubled if patients achieve benefit and continue for a second month. This cost estimate does not include the costs incurred from the adverse events that will occur in patients older than 50 years secondary to polypharmacy adverse effects and the well-described adverse effects of somnolence and dizziness leading to falls and injuries.

Finally, 2 very large randomized placebo-controlled trials of the zoster vaccine in adults aged 50 to 59 years and adults older than 60 years revealed a significant reduction in PHN in those subjects who received the vaccine.4,5 The results of these trials have led the US Food and Drug Administration to approve the zoster vaccine for all immunocompetent adults older than 50 years.3 The current rate of vaccination in eligible adults

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