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Conjoint analysis: a novel, rigorous tool for determining patient preferences for topical antibiotic treatment for acne. A randomised controlled trial

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Summary

Background Acne vulgaris is an extremely common skin disorder that can be treated effectively with drugs that are currently available. Poor compliance, however, is a major factor in the high failure rates seen in acne treatment. Compliance might be enhanced by considering patient preferences for acne medications. Conjoint analysis is well suited for the study of patient preferences in healthcare, but is novel to the field of dermatology.

Objectives The study aimed to determine and compare patient preferences for four topical antibiotics used for 1 week, once or twice daily, to treat acne vulgaris.

Methods A randomised, phase IV, single-centre, cross-over study was performed using conjoint analysis and a traditional patient questionnaire. Over 4 weeks, the patients used each of four topical antibiotics for 1 week: erythromycin/zinc solution, clindamycin phosphate lotion, benzoyl peroxide (BP)/erythromycin gel (each applied twice daily) and clindamycin phosphate gel (applied once daily). The conjoint analysis examined five different attributes of acne medications: form, storage, product life once opened, method of application and regimen (each with two or three possible options). From 108 possible permutations of the five attributes, 16 hypothetical medications were selected at random and described on printed cards. Pre- and post-treatment, the patients ranked the cards in order of preference and rated each hypothetical product based on their likelihood to use it. For each patient, product 'utilities' were then calculated by multiple regression. The patients also completed a patient acceptability questionnaire, by which they rated the product acceptability after 1 week of treatment with each of the four topical antibiotics. The patients later ranked the medications in order of preference after using all four treatments. Adverse events were recorded in diary cards to assess tolerability.

Results Of 67 patients recruited, 64 used all four medications and completed the study. The conjoint analysis found that a gel formulation, room temperature storage, product life of up to 18 months once opened, application with fingers and once-daily regimen were the options ranked first for the five product attributes. According to the ranking order (out of 108) for the combination of attributes representing the four study medications, clindamycin phosphate gel had the highest rankings (6 and 1 pre- and post-treatment, respectively) and BP/erythromycin gel had the lowest rankings (93 and 70 pre- and post-treatment). The rankings of clindamycin phosphate lotion and erythromycin/zinc solution worsened from pre- to post-treatment, indicating a shift in patient preference after they experienced products 'in-use' during the study. Based on the questionnaire,

clindamycin phosphate gel was liked best by the highest proportion of patients (33%). In terms of overall satisfaction, the order of preference was: (i) clindamycin phosphate gel, (ii) clindamycin phosphate lotion, (iii) BP/erythromycin gel and (iv) erythromycin/zinc solution. Adverse events related to medication occurred most frequently with erythromycin/zinc solution and BP/erythromycin gel. Clindamycin phosphate gel was the only product not associated with any episodes resulting in a change of medication or dose.

Conclusions Conjoint analysis provided a convenient, reliable tool for assessing patient preferences for topical antibiotics used to treat acne. The patients clearly preferred a gel formulation that could be applied with the fingers once daily and stored at room temperature for as long as 18 months. One product (clindamycin phosphate gel) combined all five of the preferred attributes, a preference confirmed by the simulated product rankings. These findings of the conjoint analysis are consistent with the safety profiles and the results of the traditional questionnaire.

Acne vulgaris is a common skin disorder that is experienced by most people at some stage during their lifetime[1] and accounts for approximately 25% of patient visits in private dermatology practice in the U.S.A.[2] During the last 20 years, the number of topical and systemic drugs available for the treatment of acne vulgaris has increased,[3] with many offering good efficacy.

Poor clinical response to acne treatment can result from factors such as poor compliance, inadequate duration of therapy and resistance of *Propionibacterium acnes* to the antibiotic administered.[4] In dermatology, poor compliance with treatment is a well-recognized problem, and it is believed that 30–40% of patients using topical formulations fail to comply with their treatment regimen.[5,6] While the reliable distinction between noncompliance and nonresponse is a new issue for medicine, the high failure rates in acne treatment appear to be linked directly to the poor compliance observed. As with prescribed treatment for any disorder, poor outcome adds extensive costs to the healthcare system.[7] Therefore, physicians need to make a careful examination of treatment compliance before investigating possible pharmacological reasons for drug failure or initiating alternative treatments and special diagnostic tests.[7]

Noncompliance is an especially important problem in treating adolescents, and the success of treatment depends not on their parents' involvement but rather on the patient's own implementation of the regimen.[8] Motivating patients to adhere to treatment is a constant challenge. The greatest success seems to result from a multifactorial approach that combines nonpharmacological interventions (e.g. patient education and rewards, medication reminders, self-monitoring and peer support) with effective, well-tolerated and simplified drug regimens.[9] Another key to compliance is the patient–physician interaction.[10,11] The formation of a 'therapeutic partnership' between physician and patient can promote compliance,[12] and some authors have encouraged clinicians to consider the importance of patient preference and therefore offer patients a choice of acne formulation.[10,11]

Conjoint analysis is a well-established research technique used to predict the choices people will make when faced with a number of products that vary in terms of specific features or attributes.[13] This technique has been used extensively in economics, psychology, marketing and statistics,[13,14] but it is also particularly well suited for the study of patient preferences and how patients perceive and respond to the salient features of medical treatments.[15] Established as being both internally consistent and internally valid, conjoint analysis allows physicians to take account of patient preferences and product attributes beyond health outcomes.[16,17] Ryan and Farrar completed a systematic review of databases (Medline, Embase, HealthSTAR, PsychLIT and EconLIT) between 1989 and 1999[18] and revealed numerous examples of the application of this method in healthcare. The authors concluded that 'conjoint analysis is a rigorous method of eliciting preferences…and allows estimation of the relative importance of different aspects of care, the trade-offs between these aspects, and the total satisfaction and utility that respondents derive from healthcare services'.

In recent years, conjoint analysis has been used widely and successfully to assess patient preferences for treatments ranging from haemodialysis[19] and anti-inflammatory drugs[20] to human immunodeficiency virus testing[21] and hearing aids.[22] The current paper, however, appears to represent the first study applying the method of conjoint analysis in the field of dermatology.

The primary objective of this study was to determine patient acceptability of four topical antibiotic products when used for 1 week, once or twice daily, to treat acne vulgaris. Product acceptability was determined using a self-administered patient acceptability questionnaire by which patients graded each treatment in order of preference. Other endpoints of the study were a conjoint analysis of the patients' product preferences, the level of product use, safety and tolerability.

Patients and methods

Study design

This randomized, phase IV, single-centre, cross-over study was designed to compare the acceptability of four established topical antibiotics during 1 week of treatment for acne vulgaris. Three of the treatments are licensed for use twice daily and the fourth for use once daily. The study centre (Inveresk Consumer Research Unit, Edinburgh, U.K.) is a clinical trial unit experienced in the conduct of phase IV studies and was able to recruit the required number of patients during the 1-month recruitment period (by local advertisement). The study was approved by the Inveresk Research Ethics Committee prior to patients entering the study. The cross-over study design made it possible to use a smaller number of patients for the treatment comparisons because each patient acted as his/her own comparator.

Patients

Seventy patients were to be recruited in order that 65 patients would be evaluable for the primary variable of assessment of product acceptability. This sample size was chosen to ensure that a certain percentage point difference in preference between clindamycin phosphate gel and the next preferred product would be significant. The study's inclusion criteria specified male and female patients aged 16–40 years with mild-to-moderate acne graded between 1·0 and 7·0 on the Leeds revised acne grading system.[23] Patients with acne conglobata, acne fulminans, sandpaper acne, submarine comedonal acne or secondary acne were excluded. The use of topical or systemic antibiotics or topical antimicrobials within the previous week was not allowed; however, these patients could enter the study following a washout period of 1 week, if all other eligibility criteria were satisfied. Patients giving informed written consent were screened for eligibility at visit 1 by determining their acne grade. At visit 2 (baseline, week 0), medical history, including previous acne therapy, and all concomitant medications were recorded. All women of childbearing potential were asked to undergo a urine pregnancy test (which had to be negative), and sexually active women were required to use adequate contraception (combined oral contraception, barrier methods, intrauterine device, depot injection) throughout the study. Eligible patients were randomised and allocated a unique treatment number.

Treatments

The four medications used in the study were: (i) treatment A: Zineryt® topical solution (erythromycin 40 mg and zinc acetate 12 mg mL^{-1}; Yamanouchi Pharma Ltd, West Byfleet, U.K.), MA No. PL0166/0109 (applied twice daily); (ii) treatment B: Dalacin T® topical lotion (clindamycin phosphate equivalent to clindamycin 10 mg mL^{-1}; Pharmacia Ltd, Milton Keynes, U.K.), MA No. PL00032/0156 (applied twice daily); (iii) treatment C: Benzamycin® gel [benzoyl peroxide (BP) 5% w/w and erythromycin 3% w/w; Bioglan Laboratories Ltd, now Schwarz Pharma Ltd, Chesham, U.K.], MA No. PL4438/0063 (applied twice daily); and (iv) treatment D: Zindaclin® 1% gel (clindamycin phosphate equivalent to clindamycin 1% w/w; Strakan Ltd, Galashiels, U.K.), MA No. PL16508/0011 (applied once daily).

Over a period of 4 weeks, every patient was to use each of the four products for 1 week. This period was considered sufficient time to allow the patients to evaluate product acceptability. For each patient, the order of the four study treatments was randomised to reduce bias in the assessments. These topical treatments have minimal carry-over effect, and the attributes being assessed over each 1-week period did not relate directly to efficacy. A washout period between the treatments was therefore not required.

At visit 2 (week 0), the first randomised medication was dispensed to the patient, who then applied it for 1 week according to product-specific dosing instructions from the patient information leaflet for the corresponding medication. In addition, patients were given the following instructions: 'Gently wash the affected area, rinse with warm water and gently pat dry. Do not scrub your skin and use only mild soaps or cleansing agents. If you do miss an application, reapply the treatment as soon as you remember, but leave about 3 hours before you use it again'.

After 1 week of treatment, the patient crossed over to the next randomised medication. This process was continued for a total of 4 weeks, with the medications dispensed to patients on a weekly basis. Patients were instructed to follow the same skincare routines and to use the same skincare products (e.g. soap, face-wash or moisturiser) for the entire study. Any changes in skincare routine, as well as adverse events and concomitant medications, were recorded.

Blinding

The marketed names of the medications were not revealed to the patients. For purposes of blinding, each medication was removed from its outer packaging, relabelled, and placed in new outer packaging, which was labelled A, B, C or D. Because the medications were not identical in presentation, appearance, frequency or mode of application, complete blinding was not possible. However, the study personnel who performed the clinical assessments did not handle any of the medications and therefore remained blinded to the medications being used by patients. Personnel who did not conduct any study assessments dispensed study medication and instructed patients on the use of medication.

Assessment of product acceptability and preference

Product acceptability and preference were assessed using a self-administered patient acceptability questionnaire, conjoint

analysis, and the measurement of product use based on weighing the medications when dispensed and on return.

Patient acceptability questionnaire

At the start of the study (visit 1), patients were given a sample questionnaire and asked to consider the questions each time they applied treatment during the week between visits 2 and 3. At visit 3, they were asked to complete the questionnaire based on the acceptability of the product that they had used during the previous week. At visits 4, 5 and 6, this process was repeated for the other three products.

The questionnaire asked three sets of questions. Firstly, the patients were asked to assess the acne product they had used during the previous week in terms of how closely it matched the following six statements: (i) 'The texture/consistency of the product was acceptable'. (ii) 'The product was absorbed easily into the skin'. (iii) 'The product smelled OK'. (iv) 'The product made my skin feel uncomfortable'. (v) 'Make-up/facial skincare products were easy to put on after application of the product'. (vi) 'Overall, I am happy with the product'. For each statement, patients were to rate the product on a scale of 0–50, in increments of 1. A score of 0 indicated that the patient completely disagreed with the statement, and a score of 50 indicated that they completely agreed with the statement. Secondly, patients were also asked to comment on what they liked and disliked about each of the products. Thirdly, after completing the four treatment periods, each patient was asked to reflect on the four different acne products and to write down the product codes in order of preference, starting with the product they liked best.

Conjoint analysis assessment of product preferences

Conjoint analysis assumes that a product can be broken down into various characteristics ('component attributes') and that the overall value ('utility') that individuals place on any product is equal to the sum of the values (or 'utilities') of all the product's attributes.[24] Product preferences are ascertained by having individuals rank and/or rate the products based on the component attributes, or in some cases individuals choose their preferred product ('discrete choice').[18]

In this study, five different attributes of acne medications were identified: form, storage, product life once opened, method of application and regimen. Two or three possible options (or levels) were assigned to each attribute (Table 1). From the 108 possible permutations of the five attributes, 16 hypothetical medications were selected at random. A description of each hypothetical medication, including the selected option or level for each of the five different attributes, was printed on to cards (16 in total).

At visit 2 of the study (before the start of treatment), patients were given the 16 cards corresponding to the 16 hypothetical products. Patients were asked to read each card carefully and to consider how easy they would find each product to use and what they liked and disliked about it. Then they were asked to: (i) sort (rank) the cards in order of preference and (ii) rate each product (out of 100) based on how likely they would be to use it. A score of 100 represented the ideal product, and a score of 0 represented the worst.

Table 1 Possible attributes of hypothetical medications for acne

Attributes	Option 1	Option 2	Option 3
Form	Gel	Lotion/solution	Cream
Storage	Refrigerator	Room temperature	
Product life once opened	5 weeks	3 months	18 months
Method of application	Roller ball	Fingers	Pad
Regimen	Once daily	Twice daily	

To determine how experience of using the products might affect results, the patients repeated this conjoint assessment at the end of the study, after all four study medications had been used (visit 6).

For each patient, product utilities were calculated by multiple regression. The rating scores are the dependent variable for each regression, while the attribute levels (options) are the independent/predictor variables. The resultant regression coefficients are the utilities, and they were reported for the study populations by averaging across all patients.

Conjoint analysis enables the investigator to simulate the 'likelihood to use' any combination of product attributes not actually shown to the respondent. Simulations for all 108 possible permutations of acne medication were calculated using the regression equation: Score = Constant + Utility for 'Form is a gel or lotion/solution or cream' + Utility for 'Storage is in refrigerator or at room temperature' + Utility for 'Product life is 5 weeks or 3 months or 18 months' + Utility for 'Method of application is roller ball or fingers or pad' + Utility for 'Regimen is once daily or twice daily'.

For example, to simulate the score for erythromycin solution, the utilities for the attributes that make up its product description were summed together with the constant.

Diary card

At visits 2, 3, 4 and 5, patients were given a diary card on which to record the time of each treatment application. Each patient was also asked to record information about any additional medication taken during the study, details of the skincare regimen used in the morning and evening, and any illness or unusual symptoms experienced. The completed diary cards were returned at the following visit, and the key information was transcribed into the case report form.

Treatment compliance

Product acceptability was also assessed based on patient compliance with treatment, which was determined using: (i) time of each treatment application recorded on the diary card; (ii) number of missed doses of study medication, as recorded in the case report form; and (iii) estimation of product usage over time (weight when dispensed minus weight when returned after use).

Safety/adverse events

All local and systemic events were recorded. At each visit, patients were asked if there had been any problem with the treatment and if they had felt different since the last visit. Adverse events reported in the patient diary cards during the study treatment period were recorded in the case report form.

Analysis methods

The intention-to-treat (ITT) population, consisting of all randomised patients, was to be the main population for the evaluation of product acceptability. However, the primary variable could be assessed only in those patients who had used all four study medications (i.e. in the per protocol population). This population represented more than 90% of the ITT population and was used in all analyses, apart from the calculation of mean scores from the patient acceptability questionnaire.

Paired comparison t-tests were conducted to establish whether the differences between clindamycin phosphate gel and each of the other three medications were significant in the analysis of data from the patient acceptability questionnaire. Differences that were significant at the 90% and 95% levels were highlighted. For the pre- and post-treatment conjoint assessments, multiple regression was used to analyse the likelihood to use each of the product attributes. Analyses of data from the patient acceptability questionnaire and the two conjoint assessments were performed using the statistical package SPSS version 6.1 (SPSS Inc., Chicago, IL, U.S.A.; April 1996).

Results

Study patients

Of 67 patients (25 males and 42 females) recruited, 64 used all four of the medications and completed the study. Three patients withdrew from the study, two because of adverse events unrelated to the study treatments and one as a result of voluntary withdrawal. Two additional patients discontinued use of one of two study medications (clindamycin phosphate lotion or BP/erythromycin gel) due to adverse events, but they both remained in the study. The median age at study entry was 23 years (range 16–40), and the median age at acne onset was 14 years (range 8–34). The median duration of acne was 8 years (range < 1–24), and the median acne grade at visit 1 was 1·75 (range 1–5·5).

Product acceptability results from questionnaire

Order of preference

The primary variable for the evaluation of product acceptability was the order of preference of the four study products, based on the patient acceptability questionnaire completed by patients following 1 week of treatment with each product. As shown in Table 2, clindamycin phosphate gel was the medication liked best by the highest proportion of patients (33%), while erythromycin/zinc solution was liked least by the highest proportion of patients (36%). The differences in order of preference did not reach statistical significance.

Product scores

For the patient ratings of the strength of their agreement with the six statements about the products, the scores (out of 50) were converted to percentages by multiplying by 2. The mean scores are presented in Table 3. There were no statistically significant differences between the four medications in terms of the acceptability of their texture/consistency. Clindamycin phosphate lotion was significantly less easily absorbed than the other three products. The smell of clindamycin phosphate

Table 2 Patient acceptability questionnaire: order of preference

	Number of patients (%) (n = 64)			
Preference	Erythromycin/zinc solution	Clindamycin phosphate lotion	BP/erythromycin gel	Clindamycin phosphate gel
Liked best	13 (20%)	17 (27%)	13 (20%)	21 (33%)
Liked 2nd best	16 (25%)	13 (20%)	20 (31%)	15 (23%)
Liked 3rd best	12 (19%)	18 (28%)	18 (28%)	16 (25%)
Liked least	23 (36%)	16 (25%)	13 (20%)	12 (19%)
Total	64 (100%)	64 (100%)	64 (99%)[a]	64 (100%)

BP, benzoyl peroxide. [a]As a result of rounding to no decimal places, 1% is effectively 'lost'.

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