

Treatment of acne vulgaris with 2 mg dienogest/0.03 mg ethinylestradiol: satisfaction among Portuguese women

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ABSTRACT

Background: Acne vulgaris is a skin disorder with severe psychological effects, including low self-esteem, anxiety and suicidal ideation. More than 85% of adolescents suffer from acne and it often persists into adulthood. Although the pathogenesis is not well understood, the pilosebaceous unit is involved. Thus, hormonal control of the sebaceous glands constitutes a treatment option. Dienogest/ethinylestradiol, a combined oral contraceptive, has proved effective in reducing acne but satisfaction with its use has not been surveyed among Portuguese women.

Objective: To evaluate satisfaction, among Portuguese women, with the use of an oral combined hormonal contraceptive, containing 2 mg dienogest/0.03 mg ethinylestradiol (Sibilla®), for the treatment of moderate acne.

Study design: Prospective, multicentric, observational study conducted at Portuguese private clinics, for which 103 women were recruited, aged between 18 and 45 years, and diagnosed with moderate acne, with indication for 2 mg dienogest/0.03 mg ethinylestradiol. At baseline, 3, 6 and 12 months into treatment, participants reported acne severity, lesion counts, skin type and skin comfort, as well as treatment satisfaction and intention to continue with it in the long term.

Results: 103 participants were recruited at baseline and 54 reached the 12-month study endpoint (12M). At 12M, a 63% reduction in the average total lesion count was observed, with comedones showing the most significant reduction (with the average count falling from 43 to 21, p -value=7.54E-08). The numbers of papules (p -value=0.005), pustules (p -value=4.43E-05) and nodules (p -value=0.0383) also decreased at all timepoints. In terms of severity, 68.5% of participants rated their skin “Clear” or “Almost Clear” at the study endpoint. At 12M, 88.9% of the women declared themselves “Satisfied” or “Very Satisfied” with 2 mg dienogest/0.03 mg ethinylestradiol treatment, and 85.2% intended to continue with it in the long term.

Conclusions: The continued use of 2 mg dienogest/0.03 mg ethinylestradiol reduced inflammatory (comedones) and non-inflammatory (papules, pustules and nodules) acne lesions in reproductive-age women between 18 and 45 years of age, previously diagnosed with moderate acne. The vast majority of participants were at least “Satisfied” with the treatment and expressed their intention to continue with it in the long term.

KEYWORDS

Acne vulgaris, dienogest/ethinylestradiol, satisfaction, observational study, skin comfort, lesion count.

Introduction

Acne vulgaris, or acne, is a common skin condition that affects 9.4% of the world population^[1]. More than 85% of adolescents suffer from acne, which is moderate to severe in about 15–20% of patients^[2]. Acne often persists into adulthood. 64% of individuals in their 20s and 43% of individuals in their 30s show signs of visible acne. A study of more than 2000 adults demonstrated that 3% of men and 5% of women still had definite mild acne at the age of 40 to 49 years^[2].

Acne can be of non-inflammatory or inflammatory type. The first is characterized by open or closed comedones, which are small papules with or without a central black keratin plug, respectively^[3]. The inflammatory type is categorized by pap-

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ules, nodules and pustules. Both types may coexist^[3] but inflammatory acne is the most common chronic inflammatory disease in adolescents and young adults^[4].

Acne results in physical symptoms such as soreness, itching, and pain, but its main effects are caused by the visible lesions in the skin. Since this is an organ on social display^[5], the

psychological effects of acne can be devastating and may lead to low self-esteem, anxiety, suicidal ideation, shame, embarrassment and social inhibition^[5].

Although the pathogenesis of acne is not fully understood, it is commonly accepted that it involves hair follicles in the skin associated with the pilosebaceous unit, an oil gland. The distribution of acne corresponds to the highest density of pilosebaceous units in the face, neck, upper chest, shoulders, and back^[5]. Several factors are implicated in acne pathogenesis, such as (1) keratin plugs blocking sebum outflow to the skin surface, (2) hypertrophy of sebaceous glands during puberty under the influence of androgens, (3) *Propionibacterium acnes* converting sebum-containing lipids into proinflammatory fatty acids, and (4) secondary inflammation of the affected follicle^[3].

Since sebaceous glands are androgen dependent, hormonal control reduces the sebum production that is initially induced by androgens. Available treatments therefore include hormonal control, but also antimicrobial therapies, vitamin A derivatives, such as 13-cis-retinoic acid (isotretinoin), and physical therapies (electrocauterization, cryotherapy and comedone extraction). Currently, there is also a considerable choice of alternative and complementary medicines^[6].

Combined oral contraceptives are indicated in female adolescents and women of childbearing age who suffer from moderate or severe acne^[5]. Several studies have demonstrated the efficacy of dienogest/ethinylestradiol for the treatment of acne vulgaris^[4,7,8]. Ethinylestradiol is a synthetic hormone derived from estradiol which reduces ovarian androgen production and stimulates liver production of sex hormone-binding globulin (SHBG). SHBG decreases biologically active free testosterone in the female body, ultimately reducing activation of the sebaceous glands. Dienogest is a fourth-generation progestin that blocks androgen receptors in target organs and reduces the activity of 5 α -reductase, which converts testosterone into 5 α -dihydrotestosterone^[9]. Although all contraceptives can be used to treat hormone-related acne, progestins are usually preferred because they possess no androgenic activity^[6].

Palacio-Cardona *et al.* reported that continued use of the 2 mg dienogest/0.02 mg ethinylestradiol combined oral contraceptive pill reduced inflammatory as well as non-inflammatory acne lesions in women aged between 18 and 30 years of age. It was also demonstrated that ethinylestradiol/dienogest diminished levels of hair and skin greasiness, and its overall effect was rated "good" or "very good" by 87.5% of surveyed women^[8].

The present study was conducted to evaluate satisfaction, among Portuguese women, with the use of 2 mg dienogest/0.03 mg ethinylestradiol (Sibilla[®], Gedeon Richter Plc., Budapest, Hungary) for the treatment of moderate acne. Secondary objectives included self-assessment of skin comfort and acne severity.

Methods

This was a non-interventional, prospective, multicentric study, conducted to assess women's satisfaction with the use of the combined oral contraceptive containing 2 mg dienogest/0.03 mg ethinylestradiol for the treatment of moderate

acne. The study was approved by the ethics committee and conducted in accordance with the Declaration of Helsinki.

Recruitment took place during regular gynecological appointments at Portuguese private clinics. 103 women were recruited, aged between 16 and 45 years, diagnosed with moderate acne, with indication for 2 mg dienogest/0.03 mg ethinylestradiol. The decision to prescribe the drug was clearly dissociated from the decision on whether or not to include the patient in the study, and the medicine was prescribed according to the approved therapeutic indications. Exclusion criteria included use of hormonal contraception in the last three months and women who were, at the time of recruitment, medicated with isotretinoin.

After checking fulfilment of all eligibility criteria, the women signed the informed consent form and answered a baseline (BS) questionnaire that requested information on their demographic, social and personal characteristics, as well as medical background and family history of acne. Women were followed for 13 menstrual cycles and at 3 (3M), 6 (6M) and 12 (12M) months into treatment answered another questionnaire, administered via e-mail or telephone. E-mail was the preferential contact route and only residual surveys were done via telephone. The study timeframe was from June 2018, when the first participant initiated the therapy, until March 2020, when the last participant completed 1 year of intake of 2 mg dienogest/0.03 mg ethinylestradiol. In all questionnaires, including the BS questionnaire, participants reported their skin type (oily, mixed, dry), acne lesion count, and acne severity based on self-evaluation diagrams, and also rated their skin comfort. Acne lesion count was based on a face division system proposed by Ramli *et al.*^[10]. Women were asked to count the different lesions in the six described segments. In turn, acne severity was ranked using the scale of 10 images suggested by Patel *et al.*^[11]. In addition, in the follow-up questionnaires, they were asked to rate their satisfaction with 2 mg dienogest/0.03 mg ethinylestradiol, and to indicate whether they intended to continue the treatment. Participants who withdrew prematurely from the study or who did not complete all the study procedures were not replaced.

Data analysis was performed with SPSS Statistics for Windows, IBM Corp., Version 21.0. (Armonk, NY), using the Fisher's exact test, Wilcoxon test, Friedman test and one-way ANOVA. Information about the different statistical analyses is included in the respective figure legends, table footnotes and in the following text.

Results

Demographics and BS characteristics

A total of 103 women were recruited, of whom 11 were found to be non-eligible. Participants initiated the treatment at the dosage of 2 mg dienogest/0.03 mg ethinylestradiol daily and were followed up over 13 menstrual cycles, answering questionnaires at 3M, 6M and 12M into the treatment. A total of 38 participants dropped out of the study, specifically 4 at BS, 11 at 3M, 12 at 6M, and 11 at 12M. The majority of these women were lost to follow up. The others stopped taking the medica-

tion on their own initiative (14), due to medical indication (4), or due to incomplete symptom relief (2). In total, 88 questionnaires were obtained at BS, 77 at 3M, 65 at 6M, and 54 at the study endpoint.

Table 1 summarizes information on the demographics, social and medical records of the women who answered at BS. 47 of the participants were aged 18 or 19 years and only four between 40 and 45 years. Mean body mass index (BMI) and systolic as well as diastolic blood pressure (SBP and DBP) values fell within the respective normal ranges. Only 8% of the participants were smokers and more than half (53%) practiced physical activity regularly.

Table 1 Demographics, social characteristics and baseline medical records (n=88).

AGE IN YEARS	NUMBER (PERCENTAGE)
18-19	47 (53%)
20-29	21 (24%)
30-39	16 (18%)
40-45	4 (5%)
BASELINE MEDICAL RECORDS	AVERAGE
BMI (Kg/m ²)	21.93 (±3.6)*
SBP (mmHg)	114.16 (±10.4)*
DBP (mmHg)	69.54 (±7.68)*
SOCIAL CHARACTERISTICS	PERCENTAGE
Smokes	8%
Practices physical activity	53%

BMI: body mass index, calculated; **SBP:** systolic blood pressure; **DBP:** diastolic blood pressure; (±SD)*

Acne evolution

At all timepoints, participants self-assessed the number of acne lesions per type over the entire face, including comedones (closed and opened), papules, pustules and nodules. The face was defined as the area bounded by ears, hairline and lower mandibular margin. Areas 1 cm below the eyes and around the brows and lips were excluded from lesion counting. Lesion count was reported for each of the 6 locations (forehead, nose, right cheek, left cheek, chin and neck) according to Ramli *et al.* [10]. Average total lesion counts (table 2) decreased over time, from 81.2 lesions at BS to 29.6 lesions at 12M. This decrease represents an approximately 64% reduction, indicating that treatment with 2 mg dienogest/0.03 mg ethinylestradiol was effective in decreasing the average number of lesions. Average count per lesion type and per facial zone decreased at all timepoints (table 2), and differences between timepoints were statistically significant for all lesion types and for all facial zones. In detail, nodules and pustules showed the highest average reduction from BS to 12M, 88.4% and 81.6%, respectively, and comedones the lowest (50.3%). All 6 facial zones exhibited more than 50% average reduction from BS to 12M. The neck area revealed the highest average reduction (79.1%) and the nose the lowest (51.4%).

In addition, participants assessed their acne severity using a validated visual analog scale consisting of 10 drawings of faces. These images depict acne severity, ranked into 6 classes: “Clear”, “Almost Clear”, “Mild”, “Moderate”, “Severe” and “Very Severe” [11]. Statistically significant differences in acne severity were recorded over the different timepoints, excepting between 6M and 12M (figure 1). At 12M, none of the women reported “Severe” or “Very Severe” acne and the percentage of women reporting “Clear” or “Almost Clear” skin has increased by 25.9% and 33.3% from BS, respectively. Treatment with 2 mg dienogest/0.03 mg ethinylestradiol also significantly altered the skin type (figure 2) Whereas 40.7% considered their skin oily at BS, only 22.2% did so after 12M of treatment.

Table 2 Average counts (per lesion type and total lesion count) per facial zone, at all timepoints: baseline (BS), 3 months (3M), 6 months (6M) and 12 months (12M) (n=54). All lesion type counts decreased over time and differences between timepoints were statistically significant for all types. In every facial zone, the average number of lesions decreased over time. The p-value calculated with one-way ANOVA. Reduction of average lesion count from BS to 12M was calculated as: [(average lesion count at BS – average lesions count at 12M)/average lesion count at BS]x100.

LESION TYPE	BS	3M	6M	12M	P-VALUE	REDUCTION (BS TO 12M)
Comedones	43.1	34.2	26.2	21.4	7,54E-08	50.3%
Papules	17.3	9.6	6.6	4.7	0,005	73.0%
Pustules	17.1	9.7	4.3	3.1	4,43E-05	81.6%
Nodules	3.7	2.5	0.8	0.4	0,0383	88.4%
Total	81.2	56	37.9	29.6	<0.002	64%
FACIAL ZONE	BS	3M	6M	12M	P-VALUE	REDUCTION (BS TO 12M)
Forehead	14.6	8.9	5.5	3.9	0.0002	73.5%
Left Cheek	11.7	7.2	4.9	3.2	0.0009	72.9%
Right Cheek	11.2	8.5	5.7	3.8	0.0270	65.8%
Nose	20.8	14.4	11.0	10.1	0.0024	51.4%
Chin	18.2	14.5	9.4	7.7	0.0219	57.6%
Neck	4.6	2.4	1.4	1.0	0.0038	79.1%

Figure 1 Evolution of acne severity throughout the 12-month treatment (n=54). Acne severity improved at every timepoint. Whereas 55.6% of participants reported “Moderate” acne at baseline (BS), only 9.3% did so 12 months (12M) after 2 mg dienogest/0.03 mg ethinylestradiol treatment. At 12M, 68.5% reported “Clear” or “Almost Clear” skin ($p=1.365 \times 10^{-18}$, Friedman test). 3M, 3 months; 6M, 6 months.

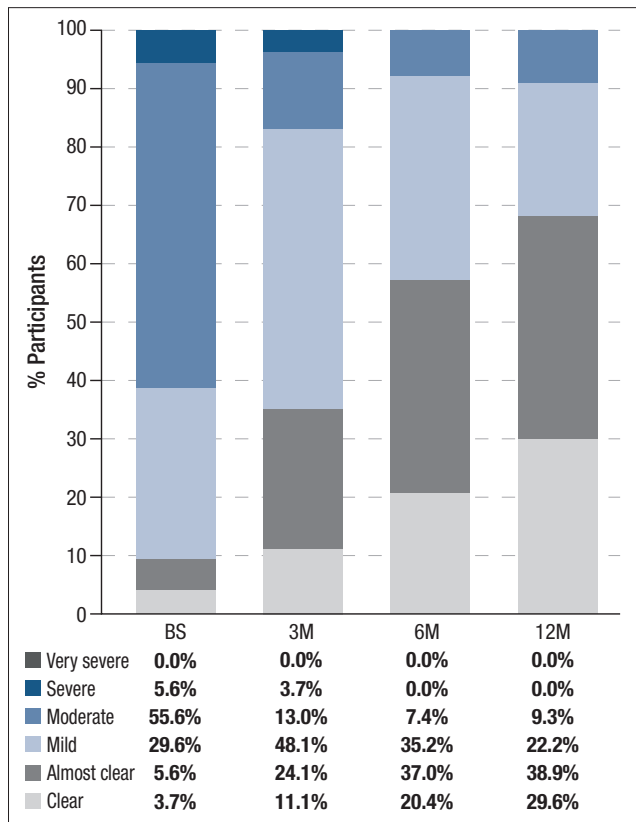
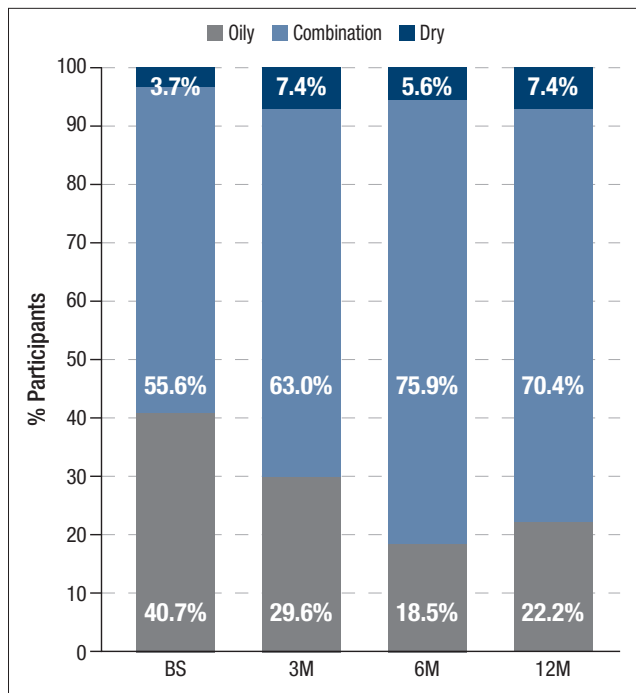


Figure 2 Percentage of participants reporting oily, mixed or dry skin at baseline (BS), 3 (3M), 6 (6M) and 12 (12M) months into treatment (n=54). Skin oiliness decreased over time. Differences over time were statistically significant ($p=0.001$, Friedman test). BS, baseline; 3M, 3 months; 6M, 6 months; 12M, 12 months.



Participants were also asked to grade their perceived skin comfort at all timepoints (figure 3). After 12M of treatment with 2 mg dienogest/0.03 mg ethinylestradiol, only 1.9% of participants did not report comfortable skin, whereas 72.2% did, representing an increase of 51.9% compared with BS comfort levels.

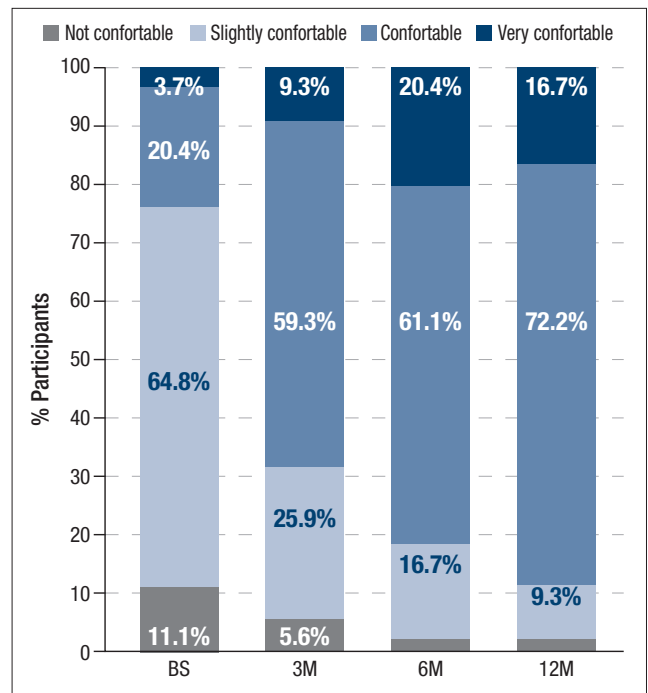
Likewise, satisfaction with skin (figure 4) increased throughout the 12M study, as demonstrated by the percentage of participants who declared themselves satisfied with their skin, which rose from 18.5% to 50.0% in the first 3 months. At the end of the treatment, 83.2% of individuals were “Satisfied” or “Very Satisfied” with their skin. In addition, there was a strong correlation between skin comfort and satisfaction with skin: $r=0.7738$ (3M), $r=0.8688$ (6M) and $r=0.9185$ (12M). These results indicate that satisfaction with skin largely depends on how comfortable it feels.

Participant satisfaction

Satisfaction with 2 mg dienogest/0.03 mg ethinylestradiol treatment (figure 5) increased over time. At 3M, 83.4% of the women already felt “Satisfied” (55.6%) or “Very Satisfied” (27.8%) with 2 mg dienogest/0.03 mg ethinylestradiol for acne treatment. At the end of the study, 88.9% of the women were “Satisfied” (42.6%) or “Very Satisfied” (46.3%). Differences in satisfaction between 6M and 12M were statistically significant ($p<0.017$, Wilcoxon test), but not between 3M and the other timepoints.

In order to understand how treatment satisfaction was correlated with other variables, Pearson correlation coefficients (r) were calculated between treatment satisfaction and (1) participant age, (2) lesion counts (total and per type), (3) acne

Figure 3 Skin comfort increased throughout the 12-month study (n=54). Participants reporting “Comfortable” skin increased from 20.4% at baseline (BS) to 72.2% at 12 months (12M) and those reporting “Very Comfortable” skin from 3.7% (BS) to 16.7% (12M). Differences over time were statistically significant ($p=4.1757 \times 10^{-13}$, Friedman test). 3M, 3 months; 6M, 6 months.



severity and (4) skin comfort (table 3), for all timepoints. As expected, satisfaction with treatment was negatively correlated with average lesion count. Satisfaction and lesion type showed a moderately strong association at 12M for papules, pustules and comedones. Otherwise, weak associations were found. Severity was also negatively correlated with satisfaction at all timepoints, presenting the strongest association among all the variables analyzed ($r=-0.566$) at 12M. At all timepoints, skin comfort perception positively influenced treatment satisfaction, but the correlation was stronger at 3M ($r=0.586$) than at 12M ($r=0.477$). Participant age was poorly correlated with satisfaction.

Further, to understand whether satisfaction with the 2 mg dienogest/0.03 mg ethinylestradiol treatment depended on other skin interventions, we examined possible relationships between daily face treatments, esthetic treatments and other medical treatments, and satisfaction at 12M. Of the 88.9% who were “Satisfied” or “Very Satisfied” with 2 mg dienogest/0.03 mg ethinylestradiol, 63% used face care treatments, such as cleansing gel, cleansing mask or anti-acne cream on a daily basis. The majority of the participants did not perform esthetic treatments (81%). Prior to the study, 24% of the participants had used another anti-acne medical treatment. Satisfaction with 2 mg dienogest/0.03 mg ethinylestradiol and reported skin comfort were independent of all types of treatments ($p>0.05$, Fisher’s Exact test).

Intentions regarding future use of 2 mg dienogest/0.03 mg ethinylestradiol

Participants were asked whether they intended to continue with 2 mg dienogest/0.03 mg ethinylestradiol treatment in the long

Figure 4 Participant satisfaction with 2 mg dienogest/0.03 mg ethinylestradiol treatment increased throughout the 12-month study (n=54). Total percentage of “Satisfied” and “Very Satisfied” patients was 88.9% at the study endpoint (12M). Differences over time were statistically significant ($p=0.032$, Friedman test). BS, baseline; 3M, 3 months; 6M, 6 months.

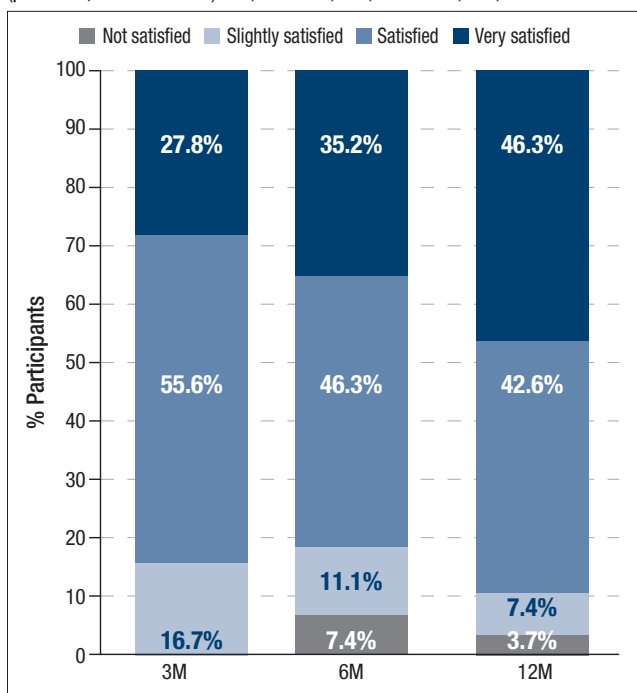


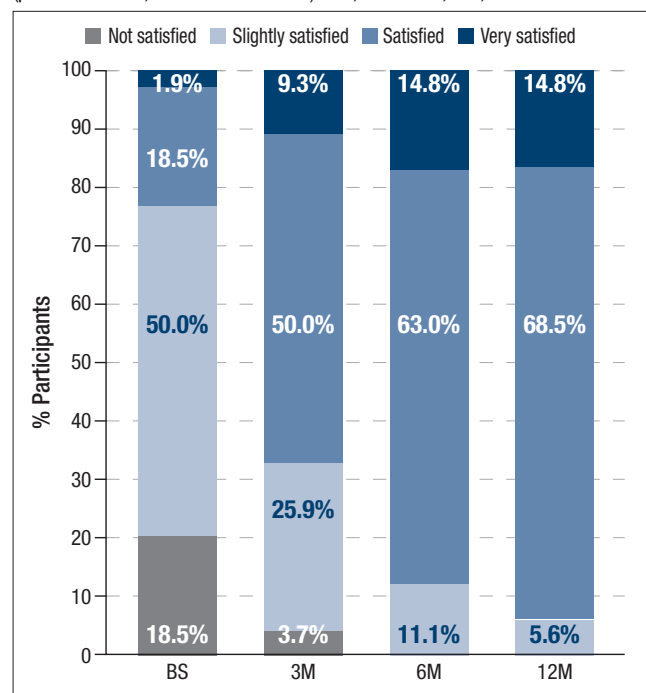
Table 3 Pearson correlation coefficient (r) between treatment satisfaction and (1) participant age, (2) lesion counts (total and per type), (3) acne severity, and (4) skin comfort, at months 3 (3M), 6 (6M) and 12 (12M) (n=54). White, light gray and dark gray cells indicate, respectively, small, moderate and strong association strength.

r	3M	6M	12M
	TREATMENT SATISFACTION		
Age	-0.08857	-0.13704	-0.14554
Nodules	-0.056	-0.278	-0.0389
Papules	-0.297	-0.253	-0.3394
Pustules	-0.254	-0.204	-0.3091
Comedones	-0.19	-0.19	-0.4005
Total lesions	-0.25676	-0.24244	-0.435099
Skin Comfort	0.586146	0.448845	0.477375
Severity	-0.54902	-0.45191	-0.565544

term. Just 3M after initiating the treatment, 92.6% of the women wished to continue with it in the long term. Interestingly, this intention was found to be dependent on the grade of acne severity. However, at 6M and 12M, the intention to continue treatment (87.04% and 85.2% respectively) was independent of the grade of acne severity.

Differences, over time, in the percentages of women intending to continue the treatment were not statistically significant ($p=0.197$, Friedman test).

Figure 5 The participants' satisfaction with their skin increased throughout the 12-month treatment (n=54). Total percentage of “Satisfied” and “Very Satisfied” participants increased from 20.4% at baseline (BS) to 83.3% at 12 months (12M). Differences over time were statistically significant ($p=1.1501E-15$, with Friedman test). 3M, 3 months; 6M, 6 months.



Discussion

Treatment with 2 mg dienogest/0.03 mg ethinylestradiol was effective in reducing all lesion types throughout the 12-month study. The average total lesion count fell by 63% and improvements in both non-inflammatory (comedones) and inflammatory (papules, pustules and nodules) acne were reported. These findings are similar to, although not as strong as, those reported by others ^[4]. In fact, Palacio-Cardona *et al.* reported a 94% reduction in acne lesions when using a combined oral contraceptive pill containing 0.02 mg of ethinylestradiol instead of 0.03 mg. The superior results of that study compared with this one might be explained by the fact that, in their study, the reported median value at BS for pustules and nodules was 0 and the oldest participant was 30 years old.

At 3M into treatment, treatment satisfaction showed the strongest association with skin comfort and acne severity. In turn, at 12M, total lesion count ($r=-0.435$) was also strongly associated with treatment satisfaction, as was comedone count ($r=-0.4005$). Thus, satisfaction showed a stronger association with the global facial appearance (severity) and how women feel about their skin (comfort) rather than with the number of facial lesions.

Complementary treatments ^[6], such as chemical peels ^[12] and light treatments ^[13], have been used for acne management. Interestingly, satisfaction was independent of whether esthetic treatment was performed during the course of the study. This fact suggests that regardless of whether or not participants performed additional treatments, the reported levels of satisfaction are primarily due to the effects of 2 mg dienogest/0.03 mg ethinylestradiol.

Cleansing gels and moisturizers have also been recommended for the daily treatment of acne ^[14]. However, in this study, treatment satisfaction was independent of whether or not participants cared for their skin on a daily basis.

Intention to continue showed a decreasing trend, which was not statistically significant. Although severity emerged as the predominant parameter influencing satisfaction, intention to continue the treatment depended on it only at 3M, and not at the subsequent follow-up timepoints.

This observation might be explained by other variables not assessed in the current study, such as decisions to suspend or change treatment, or not feeling comfortable with long-term use of hormonal treatments.

Conclusions

Continued use of the 2 mg dienogest/0.03 mg ethinylestradiol reduced inflammatory and non-inflammatory acne lesions in reproductive-age women between 18 and 45 years of age, previously diagnosed with moderate acne. Most of the women (88.9%) declared that they were at least “Satisfied” with 2 mg dienogest/0.03 mg ethinylestradiol treatment and expressed their intention to continue with it (85.2%) in the long term.

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