A double-blind, placebo-controlled, randomised, N=1 study to determine the effect of concomitant treatment with dehydroepiandrosterone (50 mg) on sexual desire in six women who experience sexual a decrease in sexual desire due to their oral contraception-use

Preliminary results

First Concept

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Abstract

Aim To evaluate the effect of dehydroepiandrosterone (DHEA) compared to placebo in oral contraceptive (OC) users on the degree of sexual desire.

Method A replicated, double-blind, placebo-controlled, single-case alternation design over 6 treatment cycles with an oral contraceptive (OC), with co-treatment of 50 mg dehydroepiandrosterone (DHEA) or placebo. Six subjects using their usual OC received as co-treatment of 50 mg DHEA during 3 treatment cycles and placebo during another 3 treatment cycles in an individualized random order, in such a way that they received a total of 3 months of both treatment types. There was a one week washout between each treatment cycle. The degree of sexual desire (0-10 scale), the main outcome measure, was assessed daily for 24 weeks.

Subjects were six healthy OC users who complained of a decrease in sexual desire since the start of OC use and who were in a satisfactory heterosexual relationship. All participants continued using their usual OC. All participants received two tablets of study medication, which were ingested daily during the first 21 days of every cycle. These tablets either contained DHEA (25 mg per tablet) or placebo. During the pill-free period (day 22 – 28), there was no intake of study medication. Total treatment duration was 6 cycles of 28 days each with a randomised monthly regimen (3 cycles placebo and 3 cycles DHEA).

Results Visual inspection of the data pattern for these six subjects suggest that there are no differences for the daily sexual desire rating between the active treatment (B) and placebo (A), except for subject 1 (p =0.07). The individual p-value for the other five subjects varied between 0.71 and 1.00 indicating no differences between active treatment and placebo. The combined p-value of the six participants was p =0.98 indicating no statistically significant treatment effect overall.

Primary Objective

The primary objective of the study was to evaluate the effect of DHEA on the degree of sexual desire during OC use. A replicated single-case alternation design was used.

Method

Design

A replicated double-blind, placebo controlled randomized single-case alternation design was used. The total treatment period was 24 weeks. Six healthy women, who met all inclusion and none of the exclusion criteria, received DHEA during 3 treatment cycles and placebo during another 3 treatment cycles in a blinded individualized random order, in such a way that they received a total of 3 months of both treatment types. There was one-week washout between treatments. During the entire treatment period subjects continued using the OC that they previously had been using.

One treatment cycle consisted of 3 weeks of daily intake of one tablet OC and two tablets of DHEA/Placebo followed by a pill-free interval of 1 week. Thus, there was one week during which subjects were not ingesting OC and DHEA/Placebo tablets between each cycle and during which a withdrawal bleeding should occur. DHEA/Placebo tablets were blinded, i.e. neither the investigator nor the subject knew whether co-treatment was an active drug or a placebo.

Medication was dispensed at each clinic visit. At each dispense, the subject received 6 blister packs of 8 tablets (25 mg) DHEA/Placebo which made a total of 48 tablets including 6 tablets for spare medication. The subject was asked to document on a daily basis whether the

study medication was taken or not. Furthermore, subjects were required to return the used blister packs during the monthly visits; this was done to check treatment compliance.

Primary outcome measure

The effect of concomitant DHEA compared to placebo in OC users on sexual desire was measured with a daily single sexual desire item: 'To what extent did you feel like having sex in the past 24 hours?' Subjects were asked to give a rating for their desire, on a 11-point scale (0 meaning 'not at all', and 10 meaning 'very much'). During every treatment cycle data were collected for all 28 days, but data obtained during the pill-free period were not used for the analysis. Per treatment type (DHEA/Placebo) data were collected for a period of 3 months (3x21= 63 and 3x7=21).

Statistics

A randomization test for single-case experimental designs was carried out to analyze the mean daily desire scores (Edgington and Onghena 2007). A randomization test is a permutation test based on random assignment to test a null hypothesis about treatment effects in a randomized experiment. In randomization tests, we consider all possible recommendations of the data, given the randomization procedure used in the design of the study. Under the null hypothesis of no treatment effect, the obtained responses would be the same under every possible random ordering. To test this null hypothesis, the test statistics for all possible data divisions are calculated, by keeping the obtained scores fixed for each measurement time, and the conditions assigned to the measurement times are randomly shuffled according to the possible orderings. The randomization test's *p*-value is then calculated by locating the observed test statistic in the randomization distribution: the proportion of test statistics that equals or exceeds the observed test statistic determines the *p*-value.

In the current study there were six measurement occasions, of which three had to be assigned to treatment A (placebo) and three to treatment B (DHEA), with the constraint of maximally 2 consecutive administrations of the same treatment there were 14 possible treatment sequences for each subject. Possible assignments were: AABABB, BBABAA, AABBAB, BBAABA, ABAABB BABBAA, ABABAB, BABABA, ABABBA, BABAAB,ABBAAB, BAABBA, ABBABA and BAABAB (A = placebo and B = DHEA). The null hypothesis of a randomization test is that there is no effect of the active treatment and thus that the observed scores are independent of the condition (A or B) in which they were observed. The first thing to do when conducting a randomization test is the calculation of the observed test statistic. For our experiment we expected that the active treatment desire scores (B=DHEA) would be higher than the scores during the placebo treatment condition (A=placebo) and thus could use as a test statistic the difference between the condition means T = (Mean $B_1B_2B_2$)-(Mean $A_1A_2A_2$).

In the present design, there were 14 possible assignments and the minimum *p*-value possibly attained was 1/14=.07 to test (Mean $B_1B_2B_2$)>(Mean $A_1A_2A_2$). To test [(Mean $B_1B_2B_2$) ≠ (Mean $A_1A_2A_2$)], the minimum p-value possibly attained was *p*=0.14. The analysis was performed using the SCRT software, Single Case Randomization Tests, version 1.1 (Onghena & Van Damme, 1994). The program allowed for the calculation of a combined *p*-value when the six participants were considered simultaneously in a meta-analysis using Edgington's additive method (Edgington & Onghena, 2007).

Results

Demographic and treatment related information

Subject	Age	Relationship duration	Used OC	Duration OC use*	Total FSFI / FSFI desire**	FDSD-R
1	24	6 years	Cyproterone / 35 EE	3 years	22.0 / 3.0	12
2	22	5 years	150 LNG / 30 EE	6 years	27.0 / 3.0	32
3	27	10 months	150 LNG / 30 EE	2 years	14.5 / 1.2	36
4	23	6 years	150 LNG / 30 EE	8 years	18.9 / 2.4	23
5	20	1.5 years	150 LNG / 30 EE	2 years	23.1 / 2.4	14
6	25	10 years	150 LNG / 50 EE	10 years	21.8 / 3.0	19

* Continuous use of OC prior to study entry
** FSFI total score cut off 26.5, range FSFI desire scale 1.2-6

Daily desire ratings

Figures 1-6 (see pages 11-16) show the daily desire ratings for each subject. Visual inspection of the data pattern for these six participants suggest that there is no differences for the daily desire rating between the active treatment phase (B) and placebo (A), except for subject 1. In subject 1, there is an indication that B is subsequently larger than A ($p = 0.07$). The individual p-values of the other five subjects varied between 0.71 and 1.00 indicating no differences between treatment phase. The combined p-value of the six participants was $p = 0.98$ indicating no statistically significant treatment effect overall (see Table 2).

Conclusions/remarks

- DHEA > Placebo in subject 1, corroborated by retrospective judgement (other subjects had 'no idea')
- DHEA efficacious in subject with most anti-androgenic OC, all others used LNG containing OC with no effects on SHBG
- In retrospect, sexual complaints in subject 3 were related to differences in desire, not OC use
- No relationship between efficacy and duration OC intake
- No relationship between efficacy and FSFI/FSDS-R scores
- We never know what people actually do 'in the bedroom' (context and stimuli)
- In N-of-1 ARC study androgens were not measured, in RCT ARC study we can study the relationship between androgens and sexuality variables

References

Edgington, E.S., & Onghena, P. (2007). *Randomization Tests,* (4th ed.). Boca Raton, FL: Chapman & Hall/CRC.

Onghena, P., & Van Damme, G. (1994). SRCT 1.1: Single-case randomization tests. *Behavior Research Methods Instruments & Computers, 26,* 369.

Table 1: Demographic data and treatment-related information of the six participants

Subject	Age	Relationship duration	OC type
1	24	6 yrs	Cyproterone/ 35EE
2	22	5 yrs	150LNG/30EE
3	27	10 mo	150LNG/30EE
4	23	6 yrs	150LNG/30EE
5	20	1.5 yrs	150LNG/30EE
6	25	10 yrs	150LNG/30EE

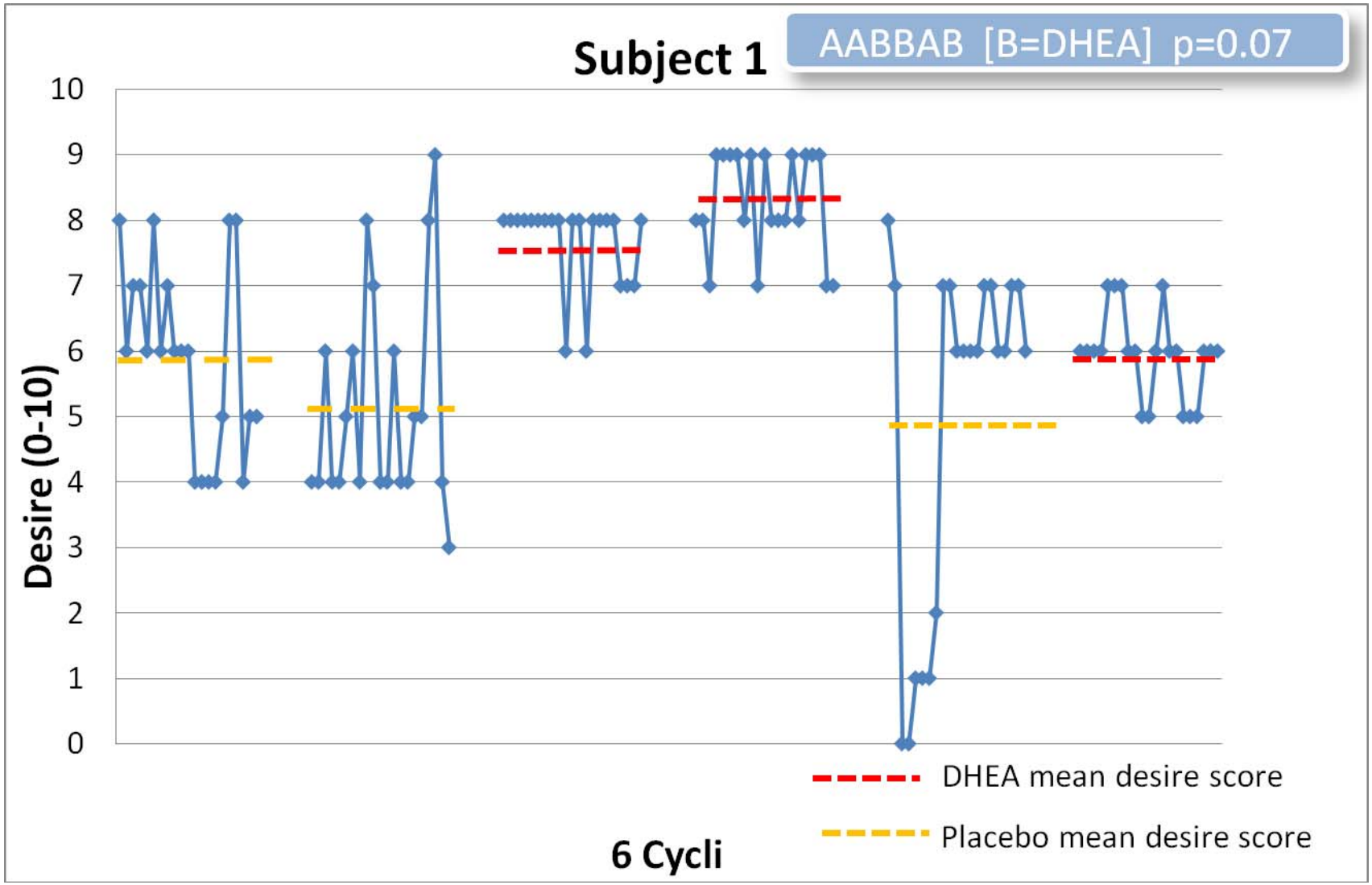

Figure 1: Subject 1, daily desire score for each condition A (placebo) and condition B (DHEA) over a period of 24 weeks

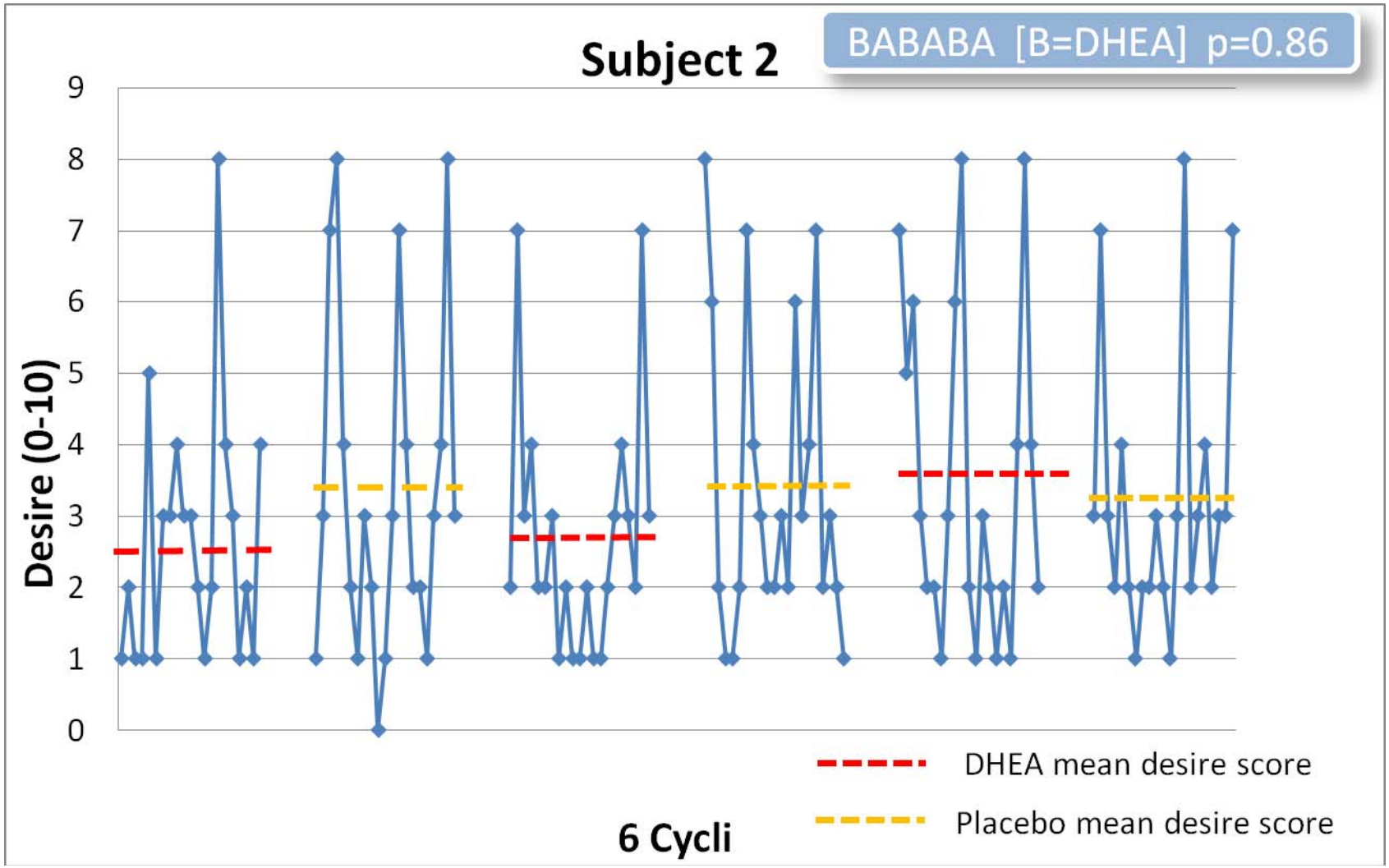

Figure 2: Subject 2, daily desire score for each condition A (placebo) and condition B (DHEA) over a period of 24 weeks

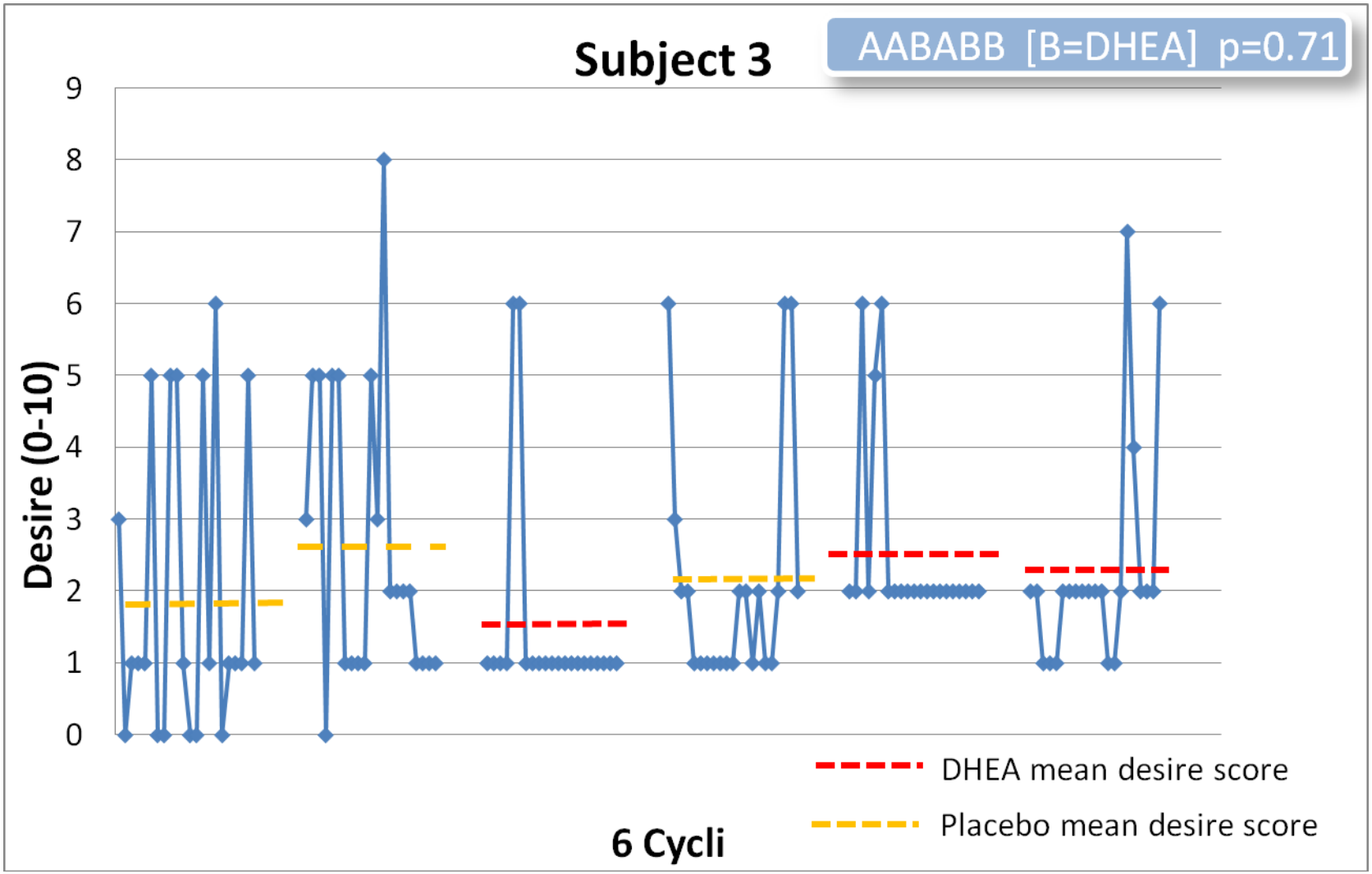

Figure 3: Subject 3, daily desire score for each condition A (placebo) and condition B (DHEA) over a period of 24 weeks

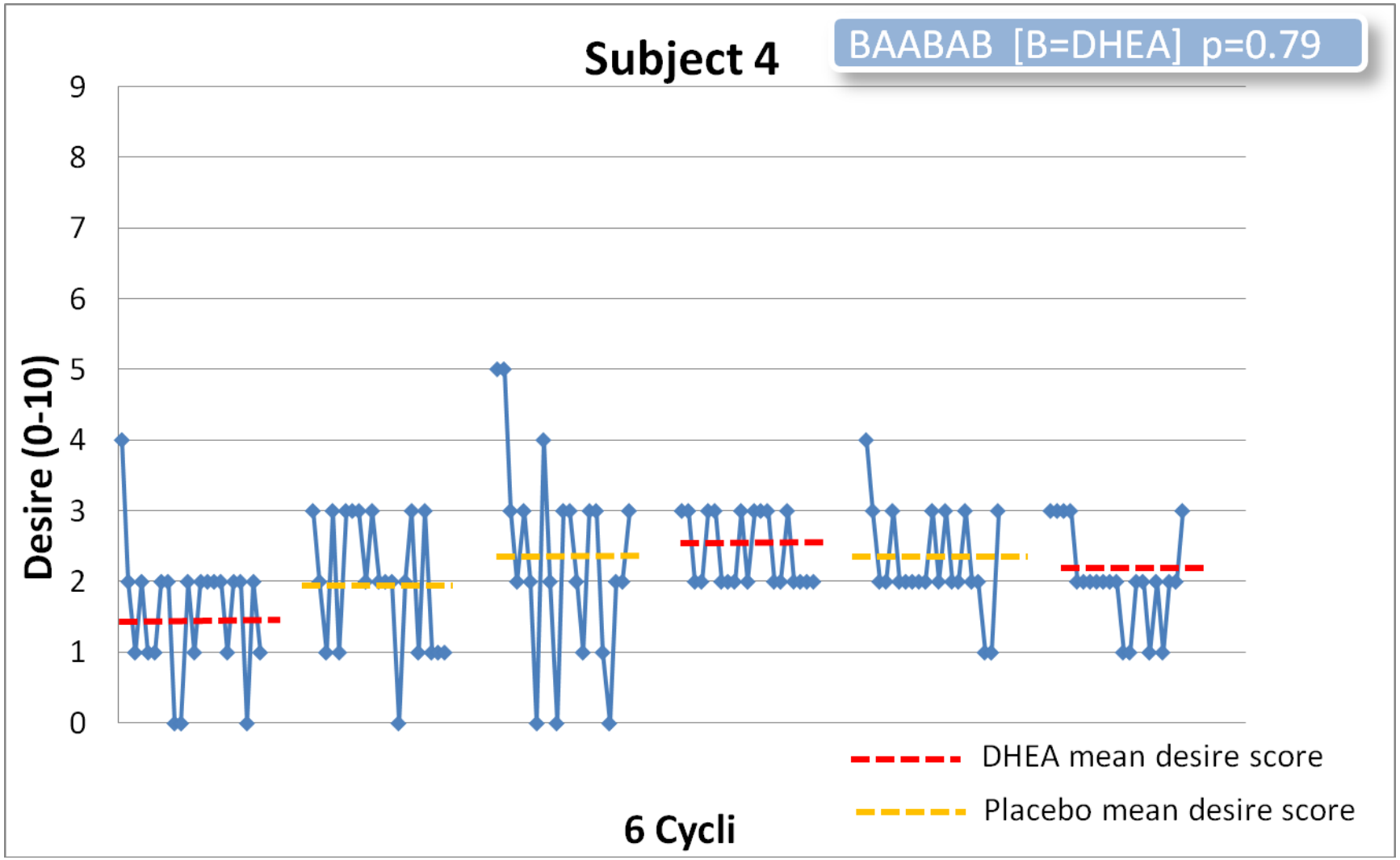

Figure 4: Subject 4, daily desire score for each condition A (placebo) and condition B (DHEA) over a period of 24 weeks

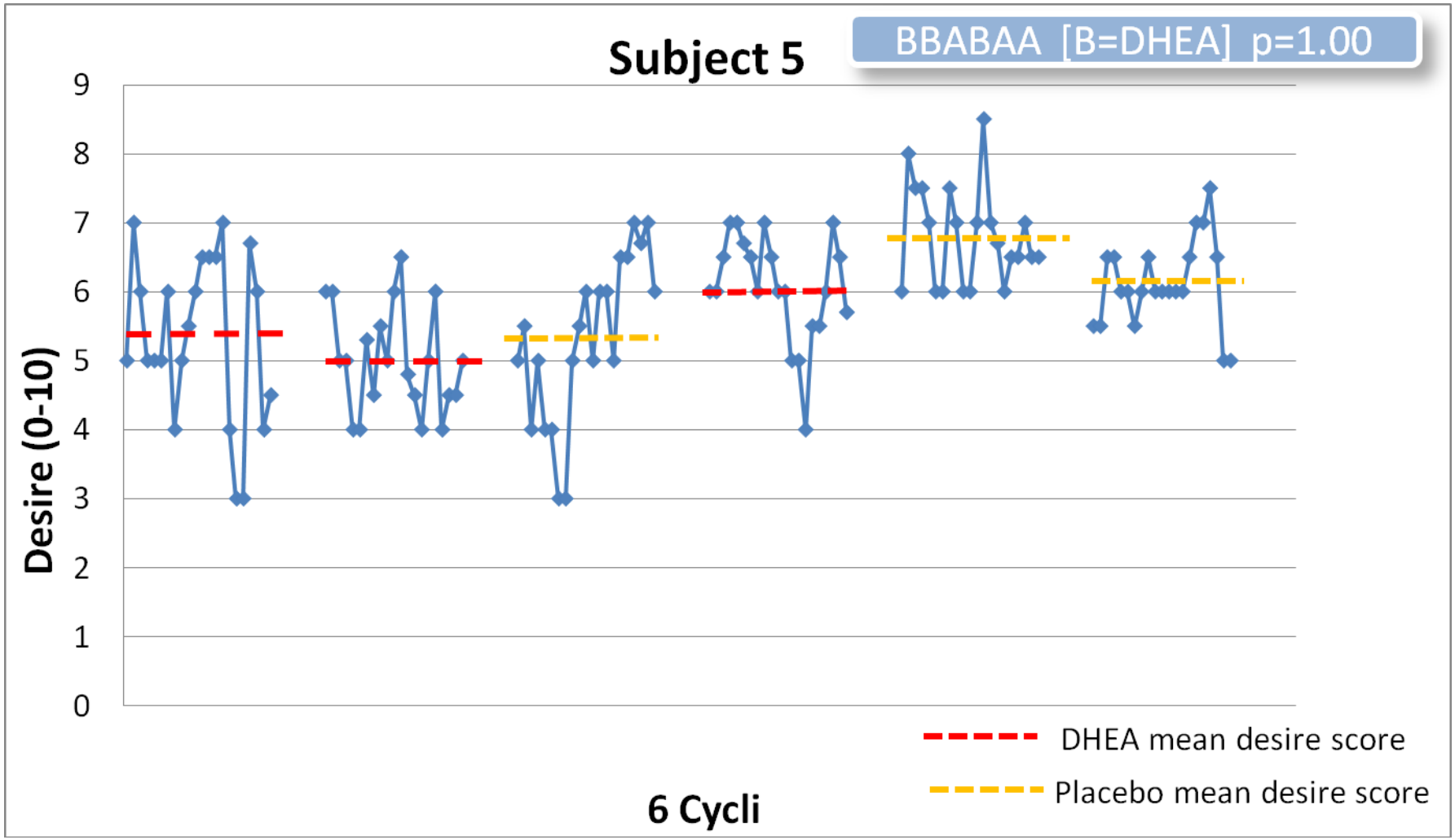

Figure 5: Subject 5 daily desire score for each condition A (placebo) and condition B (DHEA) over a period of 24 weeks

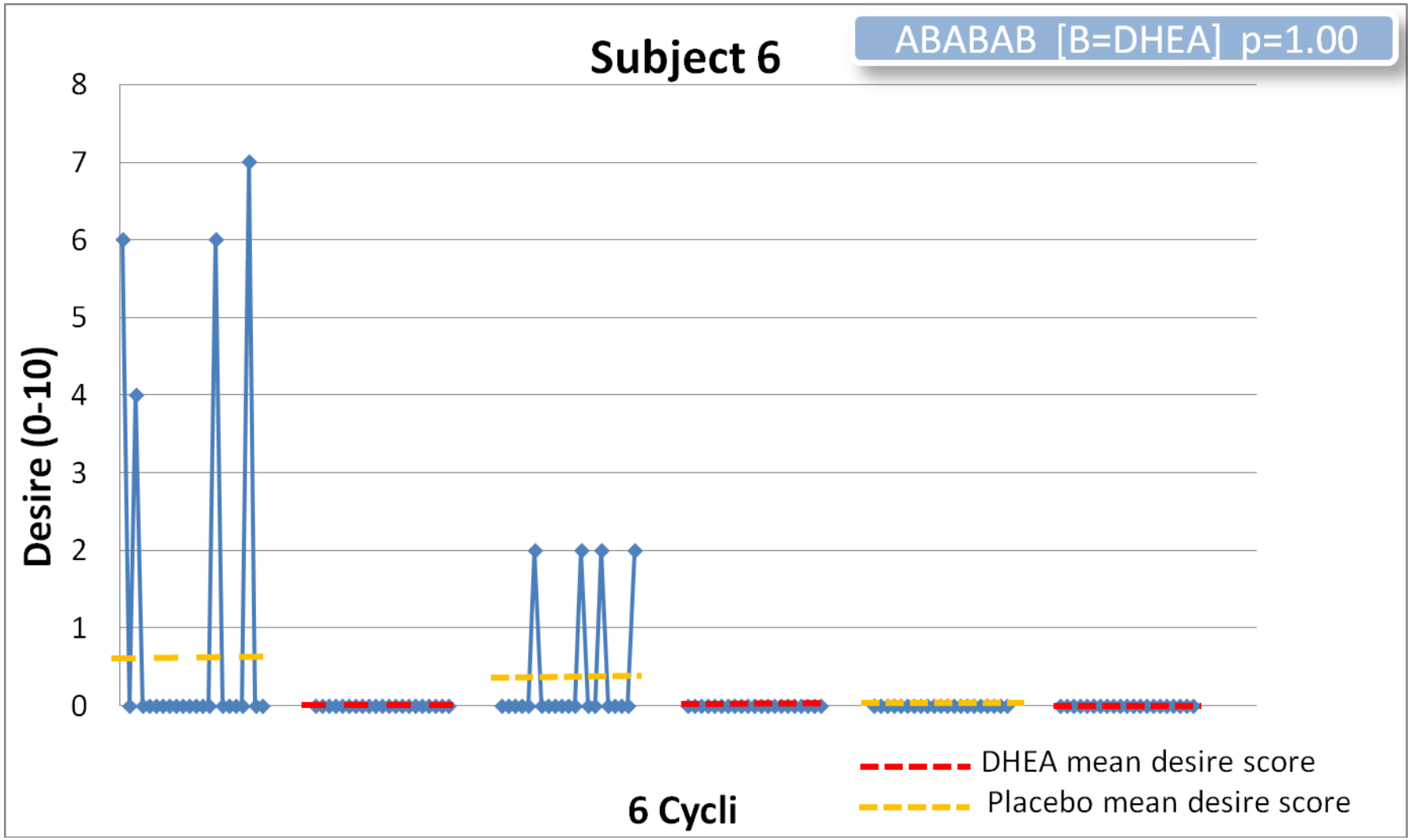

Figure 6: Subject 6 daily desire score for each condition A (placebo) and condition B (DHEA) over a period of 24 weeks