

## Sedative Effects of Placebo Treatment

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*Summary.* Observations have been made in two series of subjects on the sedative effect of a placebo given by mouth. As far as the colour of the capsules and the order of administration are concerned, males appear to react differently to placebos from females. — The incidence of side effects is the same in both males and females, the

commonest being depression of the central nervous system.

*Key-words:* Placebo, sedative agents, tablet colour, order of administration, sex-linked response.

### Introduction

Reactions to placebos are now generally accepted, but despite the extensive literature on the subject there are still many gaps in our knowledge of how and why they occur [3, 9, 12, 15].

Some authors consider that the responses evoked by placebos are wholly attributable to such physical characteristics as taste, size, shape and colour [8, 14, 17]. However, there are no authoritative references to this subject in the literature [2, 5]. Sex, age, intelligence, attitudes, habits, personality structure and educational background have also been investigated for their possible bearing on reactions to placebos [6, 10, 11, 18], as well as the particular circumstances prevailing at the time of administration, which have been considered by some [14] to be the most important components of placebo reaction.

In the course of two studies on the effects of placebos as sedatives, observations have also been made on the response of the two sexes to the colour and order of administration of capsules of placebo.

### Material and Methods

The first study was carried out with the voluntary co-operation of 56 medical students and interns (36 males, 20 females) who were in a state of emotional stress and were suffering from insomnia because of forthcoming examinations. One white placebo capsule was administered to each student on two successive evenings. They were told that they were being given two different tranquillizers.

The second study was conducted in a series of 120 hospitalized patients of both sexes, who were awaiting surgery on varicose veins (most often saphenectomy) and therefore had a mild to moderate degree of anxiety. They, too, were given one placebo capsule on two successive evenings and were told that they were receiving two different tranquillizers to help them to sleep. One capsule was blue and the other orange, two colours

widely used in commercial formulations of medicines. The sequence in which the two differently coloured capsules were given was determined by means of a table of random permutations [4], according to a cross-over design.

The capsules were taken at 10 p.m., and the following morning the subjects were asked the following questions:

1. How long did it take you to fall asleep after swallowing the capsule?
2. How long did you sleep?
3. Was it a normal sleep?
4. When you woke, did you feel you had had a normal rest?

On the second morning, the subjects were asked the same questions, and then they were asked which of the two capsules they preferred.

In both experiments, the doctor who administered the placebos and who interviewed the patients on both mornings was also told that two different tranquillizers were being tested.

### Results

In the study on medical students, the second placebo was preferred more frequently than the first (Table 1), and the majority of the subjects also believed that they fell asleep more quickly after taking the second placebo than after the first (the difference between

Table 1. Study in medical students

#### 1.1. Preferences for the 1st or 2nd placebo

	Preference for 1st placebo	2nd placebo	No preference	Total
Males	1	12	23	36
Females	5	7	8	20
	6	19	31	56

Two-tailed binomial test on the expressed preferences, without regard to sex: preferences for the 2nd placebo are significantly more frequent ( $P = 0.014$ )

sleep-induction times was found to be significant at  $P < 0.05$ ). The duration of sleep on each of the two nights however, was not significantly different. The incidence of side effects on awakening was greater with the first placebo, but the difference was not statistically significant. Thirty-one subjects did not prefer one capsule to the other.

Table 2. *Study in patients. Distribution according to sex and age*

Sequence:	Blue-Orange		Orange-Blue		Total	
	Males	Fe-males	Males	Fe-males	Males	Fe-males
Median age	22	38	31	29	53	67
	52.5	41.5	53	40	53	41

In the study with coloured capsules, sixty patients were given the blue placebo first and the orange one second, and the other sixty received the capsules in the opposite order. The distribution of these subjects according to sex and age is shown in Table 2. On average, the male patients were older than the females ( $t = 3.914$ ,  $P < 0.01$ ). In view of the discrepancy in age between the two sexes, the results were re-examined on the basis of these two factors. No evidence was found in either sex for any effect of age on preference for colour, order of administration or for interaction of such factors [16]. On the other hand, sex did show an effect of borderline significance as males appeared to

Table 3. *Study in patients. Influence of sex on results*

	Influence of sex on preferences for order of administration		Influence of sex on colour preferences	
	Males	Fe-males	Males	Fe-males
1st	14	30	Blue	16
2nd	28	24	Orange	26
	Chi-square = 3.847, $P < 0.05$		Chi-square = 4.129, $P < 0.05$	

Table 4. *Study in patients. Results according to sex and sequence*

	Blue-Orange sequence		Orange-Blue sequence	
	Males	Fe-males	Males	Fe-males
Blue	4	20	Orange	10
Orange	16	11	Blue	12
	Fisher's exact test: $P = 0.01$		Chi-square = 0.028, not significant	

prefer the second treatment and the orange capsules, whilst females preferred the first administration and blue capsules (Table 3). Colour preferences appear of greater importance if the results are considered according to the order of administration (Table 4).

The data regarding sleep-induction times and sleeping times are consistent with the expressed preferences. In this study 18 males and 6 females did not indicate any preference.

Twenty-one of 56 subjects (31.5%) in the first study, and 70 of 120 patients (58.3%) in the second complained of side effects on awakening, of restless sleep, or of both. Side effects after both treatments were reported by 17 of the total of 176 subjects (9.7%).

In the second study, 31 of the patients with adverse effects were males (58.5% of the males), and 39 females (58.2%). The data were divided according to the sex of the subjects, and by considering separately who complained of side effects on only one occasion, i.e. those from whom it was possible to obtain information about the connection between side effects and colour or order of administration [1]. It was found that the incidence of side effects was evenly distributed between the two colours, indicating that preference for a particular colour was not linked with the side effects associated with that particular colour. The incidence of adverse effects tended to differ in the two sexes depending upon the order of administration, an observation in keeping with the expressed preferences (Table 5).

Table 5. *Study in patients. Incidence of side effects*

Side effects after one administration only, according to colour and order

	Males	Fe-males		Males	Fe-males
Blue	11	16	1st	17	14
Orange	14	18	2nd	8	20
	Chi-square = 0.001, not significant			Chi-square = 3.151, $P < 0.08$	

All the subjects who described side effects complained of fatigue or drowsiness; three also mentioned having had palpitations, one reported a headache, and another nausea.

### Discussion

The statement of a preference for one or the other of the placebos could be interpreted, in a sense, as a sign of placebo reactivity; as no active compound was used, the results of the present study should be considered therefore, as applying only to placebo reactors.

Recently, Schapira *et al.* [13] have studied the effect of tablet colour in the treatment of anxiety states; although the difference between red, yellow and green tablets did not reach statistical significance, certain trends were observed, green being preferred as regards symptoms of anxiety and phobias, and yellow being preferred for depressive symptoms. On the other hand, differences in response due to sex were not considered, or were found to be unimportant [6, 7, 10].

The present observations emphasize the importance of using a cross-over design in a study based on patients' preferences. They also mean that sex may be one of the factors accounting for the responses to placebo given

as sleep-inducing agent. This point should be studied further in order to ascertain whether a sex-linked difference in response should be considered in the planning of clinical trials with sedative drugs, in order to avoid a possible source of bias.

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