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In the clinical evaluation of drug treatment, medical practitioners have long appreciated the fact that the response does not merely reflect the pharmacological effect of the drug. The manner in which the treatment is presented to the patient by his therapist is important and there is ample proof in the literature of the therapeutic effects of inert substances – the so-called placebo effects (1, 2). In psychiatric practice particularly, the halo effects of such factors are of considerable importance. The present investigation was designed to examine the possible role of tablet or capsule form of medication in the pharmacotherapy of anxiety states. The drug used was chlordiazepoxide, a widely-used anxiolytic agent of the benzodiazepine group. Its efficacy has been attested in the 'Today's Drugs' column of the *British Medical Journal* (3, 4, 5).

Forty-eight consecutive out-patients suffering from anxiety states were treated in a crossover trial with chlordiazepoxide, 10 mg three times a day in capsule and in tablet form. Each form of medication was prescribed for a period of a fortnight, the order of prescription being randomized. The tablets or capsules were dispensed eighteen in excess of those required each time. Each bottle had to be returned each time. Each bottle had to be returned before a new supply was issued. The remaining tablets or capsules were counted and recorded, thus serving as a check on the amount of medication taken by the patient during the trial period.

The diagnosis of anxiety state was defined as a condition of predominant apprehension and tension experienced mentally or physically, persisting independently of eternal factors and not considered secondary to other disorders. Chlordiazepoxide was the only drug taken by the patients during the trial period.

At the patient's first interview a clinical assessment was made, followed by a decision on availability for inclusion in the trial. Patients were told that the drugs which they would receive had been found to help others with symptoms similar to their own, but that the object of the trial was to determine which of the two was more effective in relieving these symptoms. It was also stressed to the patient that he should not reveal the type of medication. This was to keep the physician's assessment as unbiased as possible.

Before commencing treatment, evaluation of the patient's symptoms was based on Hamilton's (1959) Anxiety State Rating Scale (ASRS). At the end of the first interview the patient was asked to represent the severity of each symptom by marking a six centimeter line labeled 'absent,' 'mild,' 'moderate,' and 'severe.' This first rating was taken as a baseline representing the clinical state before trial. Later, self rating forms were filled in weekly, and the patients indicated how much the medication had helped or worsened their symptoms by marking a 12 centimeter line labeled from left to right 'very poor effect,' 'poor effect,' 'good effect,' and 'very good effect.' A patient's score is the distance in centimeters from the center of the line (no effect) to his mark divided by two (being positive on the right and negative on the left). The patient's weekly ratings were not examined until after I had completed my own assessment on the ASRS. The subsequent assessment was made after two-week intervals.

Results

Of the initial 48 patients, 4 discontinued during the first week of treatment. They withdrew because they felt worse on medication: one felt more anxious, one dizzy, and one generally worse; one was so much worse as to need admission to hospital.

There were 33 women and 11 men who completed the trial and there was no sex difference as regards duration and intensity of illness. The mean age was 32.4 years and SD 8.4. Thirty-two patients were suffering from their first psychiatric illness, whereas 12 had a history of previous psychiatric disability. The mean duration of illness was 14.5 months, median 8.4 months, range 1.2-26 months.

Medication consumption was estimated by subtracting the number of tablets or capsules returned from 60 (the number issued) and dividing the resulting figure – the number of unreturned and presumably, though not necessarily, consumed – by 14. This gave the patient's presumed daily drug consumption during the trial period of treatment. The mean daily consumption rate for capsules was 2.92 ± 0.68 (SD) and for tablets was 2.61 ± 0.45 (SD) per day.

The mean scores on the ASRS are shown in Table I. The comparison of pre-trial scores with the two periods of treatment shows a significant improvement in symptoms of anxiety over the trial period ($P < 0.01$). The difference between the two periods of treatment did not reach a significant level, but it is evident that overall responses to capsules were better than to tablets. When the patients changed to tablets there was evidence of slight deterioration, whereas when changed to capsules they continued to improve.

The patients assessed their own symptoms weekly on a self-rating scale. The total incidence of symptoms declined moderately throughout the trial. The mean of each symptom on the two ratings was calculated for each patient. The results were subgrouped according to the scores. As the number of patients in each category was rather small, for the purpose of evaluating X^2, the scores above and below +1 were pooled. Tension or Anxiety ($P < 0.05$), Irritability ($P < 0.01$), Phobias ($P < 0.025$), Broken sleep ($P < 0.05$) were significantly improved on capsules in comparison to tablets.

Of the 22 patients using capsules initially, 21 complaints were noted, and after changeover to tablets the number of complaints was 24. The other 22 patients who received tablets first voiced 18 complaints and after changeover to capsules only 12 complaints were registered. These were described as fatigue, headache loss of pleasure, irritability and drowsiness. Fifteen patients requested continuation of the same treatment while receiving treatment with capsules.

Discussion

In the treatment of anxiety the response to inert substance varies from 24 to 74 percent of the patients (6). Similar results have been found for headache, nausea, cough, seasickness and the common cold (7). Active preparations and surgical procedures also vary in their effects according to differences in expectation or environment (7, 8, 9).

While scientific evidence has been collected systematically for the effect of the expectation of the patient and his therapist in the rate of symptomatic improvement with inert or active preparations, and the pharmacology of the placebos which include close effects, time related effects, side effects (10) and even drug dependence (11), the therapeutic consequences of ancillary factors such as shape, size, taste and color of medical remedies has been surprisingly neglected.

Table I
Ratings of mean ASRS scores

		Initial		Two weeks			Four Weeks	
No. of patients		Mean	SD	Mean	SD		Mean	SD
22	Capsule	14.2	3.8	9.3	3.5	Tablet	9.9	3.6
22	Tablet	13.9	3.7	9.7	3.6	Capsule	9.0	3.1

In psychiatric practice, where placebo response is proportionately higher, such ancillary factors are of considerable importance. One interesting study of the effect of tablet color in the treatment of anxiety states is described by Schapira et al. (12). They found that patients with anxiety symptoms showed a favorable response to green tablets, while the same preparation in a yellow tablet was more effective in relieving depression.

The results obtained in this study by comparison between the mean scores of each period show an overall beneficial therapeutic response, most likely attributable to the drug rather than to any particular psychological effect, as this improvement did not change significantly from week to week.

Though the difference in beneficial effects on the physician's rating only showed a trend, the symptoms of anxiety or tension, irritability, phobias and broken sleep on the patient's ratings were significantly affected by the form of medication. The capsules were consumed more regularly, and requests for continuation of the treatment with this form of medication were made by the patients. These findings indicate that there is more psychological dependence and preference for capsules by the patients in the treatment of anxiety states, and also indicates that the form of medication can act as an important additive ancillary factor in the placebo response.

Summary

Forty-four patients with anxiety state were treated with chlordiazepoxide, which was administered in tablet and in capsule forms. Every patient received two weeks' treatment with each form according to random crossover program. The patients were assessed fortnightly on physician's ratings and weekly self-ratings. Preference for capsules was shown by increased consumption rate and on the rating scales. The symptoms of anxiety, irritability, phobias and broken sleep improved significantly on capsules on patients' self-ratings.

Results indicate that the shape of medication may play a part in the response to drug.

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