

# THE VALUE AND LIMITATIONS OF CHLORPROMAZINE IN THE TREATMENT OF ANXIETY STATES

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CHLORPROMAZINE hydrochloride (Largactil) introduced by Laborit (1952) has aroused considerable interest on account of its varied pharmacodynamic actions and clinical reports drawing attention to its possible use in anaesthesia, general medicine and psychiatry.

Chemically related to certain antihistamine drugs, it has little antihistaminic activity itself but has diverse effects on the nervous system. It is a neural depressant with central and peripheral action, vagolytic and sympatholytic properties. (Chauchard, 1952; Courvoisier, 1953; Sigwald and Boutier, 1953; Staehelin and Kielholz, 1953; Lehrman and Hanrahan, 1954; Anton-Stephens, 1954; Winkelman, 1954; Garmany, 1954; and Elkes and Elkes, 1954.)

Enthusiastic claims have been made regarding the therapeutic value of chlorpromazine in a wide variety of psychiatric disorders; many of these have failed to carry conviction, as most of the reports are based on mixed groups with an insufficient number of patients in each diagnostic category to justify definite conclusions and also because controlled procedures were rarely used.

We therefore decided to confine our investigation to one type of psychiatric disorder and chose anxiety states, since the reported pharmacodynamic actions of the drug suggested that it might be of value in the treatment of states of anxiety and tension. The total group studied consists of 150 patients all of whom are treated as out-patients.

## PLAN OF TRIAL AND METHODS

In planning the therapeutic trial it was necessary:

- (a) To ascertain the possible role played by suggestion, as distinct from the pharmacological properties of the drug, in achieving therapeutic effects.
- (b) To take into account the possibility of improvement occurring during the trial period either spontaneously or due to factors unrelated to the pharmacological properties of the drug.
- (c) To employ standardized detailed methods of recording clinical state and symptomatology so as to facilitate statistical comparison of changes during the trial period.

With these needs in mind the following methods were used:

### (1) *Double Blind Method*

It was considered essential that neither patient nor physician recording clinical changes should know when active or inert tablets were being administered.

The inert tablets used were supplied by Messrs. May and Baker and were identical in size and appearance to the 25 mgm. Largactil tablets.

The inert and active tablets were marked X or Y for identification purposes by the dispenser, the only person knowing when active or inert tablets were being administered.

### (2) *Sequence Control*

In order to control the possibility of any improvement due to factors other than the pharmacological properties of the drug and also to take into account the possibility of persistence of the pharmacological effects of chlorpromazine into the ensuing period of inert tablet administration, it was decided to give one half of the patients X tablets for the first part of the trial and Y tablets in the same dosage for an equal period afterwards and the other half of the group tablets given in reverse order.

### (3) *Clinical Assessment*

For the purpose of uniformity of recording and to facilitate detailed comparison a special item sheet was devised for the investigation. The item sheet contained information regarding the social data, family and personal history, personality, clinical state and symptomatology. Particular attention was given to the recording and assessment of various aspects of emotional tension such as verbal reports of tension, bodily symptoms of tension, somatic signs of emotional tension, neuromuscular tension and autonomic lability which were rated on a seven-point scale according to severity. Finally a composite rating of total tension was made for each patient.

This method permitted ready detailed comparison of changes occurring during and after treatment.

Clinical assessments and ratings were made as follows:

- (1) Before onset of "tablet" administration.
- (2) After treatment with X tablets.
- (3) After treatment with Y tablets.
- (4) At weekly intervals thereafter.

### CLINICAL DATA

The series of 150 patients consisted of males 49 and females 101. The age distribution was as follows: 16-25, 12 per cent.; 26-35, 30 per cent.; 36-46, 30 per cent.; 46-55, 16 per cent.; 56-65, 8 per cent.; 66-75, 4 per cent.

The patients were selected because anxiety and tension were predominant in the clinical picture. Under the diagnostic term "anxiety state" a variety of clinical syndromes are subsumed, depending on the patterns of somatic expressions of anxiety and tension and the presence of depressive, obsessional, hysterical or hypochondriacal features. The variety of symptoms occurring in the group enabled observations to be made on the effect of chlorpromazine on a number of mental and physical aspects of anxiety-tension states.

### DOSAGE

The tablets used were Largactil 25 mgm. (May and Baker) and inert tablets of identical size and appearance.

During the period of the double blind trial the following tablet dosage was applied. On the first day, one tablet and increasing by one tablet daily until three a day which was continued for fourteen days. The same dosage was

applied for both X and Y tablets. This enabled a daily dosage of 75 mgm. of chlorpromazine to be given for two weeks. The total period of the blind trial was therefore 32 days.

After the blind trial period, continued treatment was given with chlorpromazine in order to determine optimum effects and to observe changes over a longer period. In these patients the dosage was gradually increased until optimum clinical effects were achieved or until evidence of drug saturation occurred such as dryness of the mouth and marked lethargy in the day time.

There was considerable individual variation in the optimum dosage. We found that in the majority of patients a daily dosage of 75–100 mgm. was adequate but some patients needed higher doses, e.g. 200–300 mgm. daily.

The optimum dose was continued for 3–4 weeks and then gradually reduced. If symptoms returned the dose was increased again for a further period before gradual reduction and termination.

#### CLINICAL EFFECTS OF CHLORPROMAZINE

The clinical effects of chlorpromazine may be considered from the patients' subjective reports and by more objective evidence appertaining to clinical signs, the appearance and behaviour of the patients.

#### SUBJECTIVE REPORTS

About three-quarters of the patients reported an improvement in symptoms and subjective state initially. The effects were usually relief of anxiety, tension and apprehension. There is a feeling of calmness without the dulling of alertness which often occurs with barbiturates. Patients describe the change as a natural feeling of ease and calmness.

There is a tendency for energy and drive to be decreased. If dosage is increased beyond the optimum, marked lethargy and even stupor may develop. In fact the dosage must be adjusted in each patient with the aim of relieving symptoms without producing an undesirable degree of inertia or lethargy.

The reduction in anxiety, tension and apprehension is usually accompanied by increased confidence and a number of our patients who previously, on account of their anxiety states, had been unable to venture out of their homes on their own were now able to go out alone, visit places of entertainment and travel on public transport, etc.

#### APPEARANCE AND BEHAVIOUR

The beneficial changes with chlorpromazine therapy are sometimes apparent in the patient's appearance, clinical state and general behaviour even before he recognizes or reports improvement.

The tense, strained appearance of the anxious patient is replaced by a more relaxed and contented countenance. General attitude and posture more relaxed. Relatives and friends may notice that the patient is not so readily upset by the stimuli or situations which previously evoked undue emotional reactions.

Although problems and conflicts may still be present, the patient states that they do not trouble him so much as previously. Patients who during their illness were too anxious or preoccupied to read newspapers or books, listen to the radio or watch television became more interested and participated in these activities with greater enjoyment. Appetite, when impaired by anxiety and tension, improved during chlorpromazine therapy.

## SYMPTOMATIC EFFECTS

Comparison of ratings of symptoms and signs before, during and after chlorpromazine therapy revealed that some clinical features were more frequently alleviated than others.

(a) *Clinical features most frequently alleviated*

Symptoms which showed the most favourable response included general tension, anxiety and apprehension together with such bodily symptoms and signs as internal tremulousness, tremors, bowel frequency and urgency, stammering on excitement, excessive sweating and neuromuscular tension with its various symptomatic manifestations improved *pari passu* with improvement in general tension and anxiety.

(b) *Symptoms showing variable response*

Certain symptoms showed a variable tendency to improve.

Insomnia for example was improved in 50 per cent. of patients, in 40 per cent. it was not changed and in 10 per cent. it became worse. A similar distribution of therapeutic effects applied to palpitations, 45 per cent. being improved, 40 per cent. not improved and 15 per cent. made worse. Headaches were only improved in 35 per cent., 50 per cent. were not improved and in 15 per cent. the headaches became more severe. Only half of 10 patients with severe vomiting as a predominating symptom were relieved by chlorpromazine.

(c) *Symptoms showing little tendency to respond*

Postural dizziness and fainting showed little tendency to improve and in some patients developed as a new symptom with chlorpromazine. Pre-menstrual tension symptoms as a rule were not significantly relieved with chlorpromazine.

We were not able to confirm the claims of other authors that chlorpromazine given alone was particularly helpful in relieving pains, whether predominantly psychogenic or physiogenic in origin.

## SIDE EFFECTS

The following side effects and complications occurred:

(1) Dryness of the mouth occurred in most patients if the dose were increased beyond optimum.

(2) Constipation was common in early stages of drug administration but passed off without special treatment.

(3) Tachycardia and palpitations were in some patients so disturbing that treatment had to be terminated.

(4) Postural dizziness, as might be expected from the hypotensive nature of the drug, tended to occur in early stages and usually passed off after a few days. If troublesome, patients were advised to lie down for half an hour after taking the tablets. We did not consider it advisable to give this advice to all patients, as the majority did not develop this symptom and we wished to avoid drawing the patient's attention unnecessarily to the possible development of this side effect.

(5) Pyrexia of 101–103° F. in three patients.

(6) Erythematous rashes in three patients, which after drug withdrawal cleared during the course of a week or so.

No patient in our series developed jaundice, a complication which has been reported by a number of authors.

#### METHOD OF GRADING RESULTS

From the findings in clinical examination, interview ratings and assessments the results were graded as follows:

Grade		Weighting
I	Marked clinical improvement .. .. .	+3
II	Moderate clinical improvement .. .. .	+2
III	Slight clinical improvement .. .. .	+1
IV	No improvement .. .. .	0
V	Slight exacerbation of symptoms .. .. .	-1
VI	Moderate exacerbation of symptoms .. .. .	-2
VII	Marked exacerbation of symptoms .. .. .	-3

By applying weights to the different grades it is possible to make allowance for any effects obtained during the course of inert tablets.

Thus if a patient had slight improvement with inert tablets (i.e. Grade III=+1) and marked improvement (Grade I=+3) with chlorpromazine, the degree of improvement attributable to chlorpromazine would be expressed by the difference between the weighting of the respective grades, viz. +2.

#### RESULTS

The results will be described in two parts:

- (a) The results during the double blind trial.
- (b) The results obtained by treatment over a longer period.

##### *Double Blind Trial*

The gradings obtained in the double blind trial on 150 patients were as follows:

Grade	Chlorpromazine Per cent.	Inert Tablets Per cent.
I .. .. .	10	0
II .. .. .	34	2
III .. .. .	22	8
IV .. .. .	26	84
V .. .. .	4	2
VI .. .. .	4	4
VII .. .. .	0	0

The difference between percentage improved with chlorpromazine (66 per cent.) and inert tablets (10 per cent.) is of high statistical significance (critical ratio over 12).

The fifteen patients who improved during the period of inert tablet administration had the following gradings with chlorpromazine. Six patients who had slight improvement (Grade III) with inert tablets showed no additional improvement with chlorpromazine. Six patients who had slight improvement with inert tablets (Grade III=+1) had marked improvement with chlorpromazine (Grade I=+3). The effect attributable to chlorpromazine in the latter group is therefore +2 for each patient. Three patients who showed moderate improvement (Grade II) with inert tablets became considerably worse with chlorpromazine (Grades V and VI).

*Results obtained with chlorpromazine given over a longer period*

The following were the results obtained by continued trial with chlorpromazine:

Grade	Per cent.
I .. .. .	16
II .. .. .	38
III .. .. .	24
IV .. .. .	14
V .. .. .	4
VI .. .. .	4
VII .. .. .	0

The above results represent the best achieved in the series with Chlorpromazine. They must not be regarded as the final assessment as we found the relapse rate after initial improvement to be quite substantial.

*Relapses*

The following relapses occurred despite continued administration with chlorpromazine:

Of 24 Grade I patients 15 relapsed

57 Grade II patients 39 relapsed

36 Grade III patients 24 relapsed

Relapses occurred after periods varying from 2-10 weeks of improvement.

## RESULTS ON FOLLOW-UP

The position at 3-7 months follow-up taking into account relapses was as follows:

Grade	Per cent.
I .. .. .	6
II .. .. .	12
III .. .. .	8

Thus only 26 per cent. of the total group derived continued therapeutic benefit from chlorpromazine therapy and only in 6 per cent. did the effect amount to marked clinical improvement.

## DISCUSSION

The complexity of psychiatric material and the multiplicity of factors which may influence the course of a psychiatric illness make the scientific evaluation of new therapeutic agents difficult.

The utilization of controls is indispensable, but the choice of controls sometimes offers practical difficulties. Thus, the method of paired controls has inherent difficulties in psychiatry as accurate matching of patients with similar prognosis may be extremely difficult or sometimes impossible to achieve. The method of using the patient as his own control has much to recommend it especially if such methods as the double blind and sequence control procedures are utilized enabling the effect of suggestion to be ascertained and also the control of factors unrelated to the pharmacological effects of the drug.

Using these methods our results indicate that chlorpromazine has significant clinical effects attributable to its pharmacological properties.

Not all patients however were significantly improved; in fact the best results obtained even with extended trial at optimum dosages were 54 per cent. showing marked or moderate improvement and of these 66 per cent. relapsed

despite continued medication with chlorpromazine. Even in this group only certain symptoms were ameliorated. These facts indicate considerable therapeutic limitations of the drug even in anxiety tension states which some authors regard as being pre-eminently suitable for chlorpromazine therapy. Furthermore, in spite of the detailed methods used, we were unable to find precise indicators in clinical symptomatology which enabled an accurate forecast to be made indicating which patients are going to respond favourably. Clinically similar cases may show a markedly different therapeutic response to the drug. It was easier to forecast which patients are unlikely to respond favourably. Patients who were very inhibited, easily fatigued and markedly lacking in energy and initiative were not, as a rule, helped by chlorpromazine.

The occurrence of disturbing side effects is a further disadvantage, and patients should not be allowed to be in charge of machinery or vehicles until their reaction to the drug and development of possible side effects is known.

These considerations indicate the considerable limitations of the value of chlorpromazine in anxiety states and its main usefulness would appear to be for short term symptomatic treatment and management.

#### SUMMARY

1. A controlled therapeutic trial of chlorpromazine in a group of 150 patients with anxiety states is described.
2. Utilizing the double blind method and other controlled procedures it was found that the results obtained by chlorpromazine were significantly better than with inert tablets.
3. Extended trial with chlorpromazine at optimum dosages resulted in 54 per cent. of the group showing marked or moderate symptomatic improvement. Two-thirds of these patients relapsed after a few weeks of clinical improvement despite continued medication with chlorpromazine.
4. This high tendency to relapse together with the development of side effects considerably limits the value of the drug. The usefulness of Chlorpromazine in anxiety states would appear to be largely restricted to short term symptomatic treatment and management.

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