

# ACETYL CHOLINE AS A THERAPEUTIC AGENT IN MILD PSYCHIATRIC DISORDERS

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IN 1950 López-Ibor adapted Fiamberti's use of acetyl choline in schizophrenia for the treatment of psychoneurotic disorders (Fiamberti, 1940, 1950a, b; López-Ibor, 1950, 1952). Very few reports of the efficacy of this treatment have been published and they vary from the enthusiastic (Sargant, 1952; Phillips and Hutchinson, 1954) and the doubtful (Maclay, 1953), to the unequivocally rejecting (Hawkings and Tibbetts, 1956). The latter authors stressed the beneficial psychotherapeutic atmosphere of the clinic, and showed that injections of sterile water produced equally as good results as acetyl choline. This paper is a further attempt to evaluate the specific effect of acetyl choline in the treatment of mild psychiatric disorders.

## METHOD AND RESULTS

Cases referred for acetyl choline treatment were selected from a large out-patients clinic. As illustrated in Table I, the majority of these patients had

TABLE I

*Illustrating the Type of Case Referred for Treatment by Acetyl Choline and Showing that the Patients who did Not Reply to the Questionnaire were Not Significantly Dissimilar from the Others*

	73 Patients Replying to Questionnaire	37 Patients Not Replying to Questionnaire
Average age .. .. .	34·7 years	35·2 years
Average number injections .. .. .	16·4	14·8
Male/Female ratio .. .. .	31 M : 42 F	17 M : 20 F
Diagnosis:		
Depressive reactions .. .. .	45	24
Phobic } reactions .. .. .	18	4
Obsessive } .. .. .		
Anxiety reactions .. .. .	4	2
Hysterical reactions .. .. .	2	1
Others .. .. .	4	6
Duration of illness .. .. .	2·9 years	2·4 years

depressive reactions or a mild obsessive-compulsive state similar to that described by Sargant (1952). Hysterics and patients with a classical obsessional neurosis are not helped by acetyl choline treatment. Only a few patients with overt anxiety were referred, as it was found that the unpleasant side effects of acetyl choline often upset these patients and they discontinued treatment after only one or two injections.

Acetyl choline (Roche) was given in doses of 200 mg. intravenously, starting with 50 mg. and increasing over 4 weeks to the full dose. The injections were given slowly over  $\frac{1}{2}$ -1 minute so that the production of severe symptoms

or unconsciousness was avoided. The injections were given at weekly intervals for 30 weeks, though in many cases the course was curtailed. In this investigation an attempt has been made to assess firstly the incidence of improvement in patients having treatment with acetyl choline, and secondly, to assess the specific therapeutic effect of acetyl choline as distinct from the non-specific effects related to attending the clinic.

(a) In the past three years, 110 patients have had acetyl choline and the immediate effect of the treatment was assessed separately from the case notes and by means of a questionnaire. Because of the obvious difficulties, cases were rated simply as improved or not improved. Seventy-three patients replied to the questionnaire and 44 (60 per cent.) of these patients thought that acetyl choline had helped them (Table II). Thirty-seven patients did not reply to the questionnaire. These patients did not seem dissimilar to the main group (Table I). It is to be expected that these 37 patients would have rather worse results

TABLE II

*Showing the Incidence of Improvement After Acetyl Choline Treatment in 73 Patients, Comparing the Patients' Own Assessment of Improvement with the Assessment from the Case Notes*

Diagnosis	Patients' Assessment	Assessment from Case Notes
Depressive reactions .. ..	28/45 (62%)	26/45 (57.5%)
Phobic } reactions .. ..	11/18 (61%)	10/18 (55.5%)
Obsessive }		
Anxiety reactions .. ..	2/4	2/4
Hysterical reactions .. ..	1/2	0/2
Others .. ..	2/4	1/4
Total .. ..	44/73 (60%)	39/73 (52%)

than the group who replied to the questionnaire and therefore these latter could not be regarded as representative of the whole group. Theoretically, it is possible either that all these 37 patients improved, or that none improved, when the incidence of subjective improvement for the whole group would fall between 74 per cent. and 40 per cent. Perhaps a closer estimate can be made by using an assessment of improvement as judged from the case notes, where it was thought that 12 of these 37 patients had improved. However the patients who replied to the questionnaire rated themselves slightly better than we had assessed them, in the proportion 1 : 1.4. In this way an estimate can be made that 14 ( $12 \times 1.4$ ) of the 37 patients considered themselves to have improved, making an improvement rate for the whole group of 110 patients of 58 (53 per cent.).

(b) A controlled investigation was devised whereby the therapeutic effect of acetyl choline could be compared with a therapeutically inert substance, all other factors being kept equal. Calcium gluconate was selected as the control drug. It is not dangerous in the dosage used (5 ml. of a 10 per cent. solution). The side effects produced by intravenous injection of this dose over  $\frac{1}{2}$  minute resulted in a generalized feeling of warmth and a burning feeling in the throat, sensations which are similar to those produced by acetyl choline and which last for about the same length of time. Unpleasant side effects to a treatment are bound to have psychological effects which it was felt should be taken into account, and it was essential that no suspicion should be raised among the patients that the injections might differ.

Twenty-five consecutive patients referred to the clinic were given either calcium gluconate or acetyl choline, the selection being done on a random basis by means of a latin square. One of the cases failed to attend after receiving only one injection of calcium gluconate and is not included in the results. Of the remaining 24 cases, 13 had acetyl choline and 11 calcium gluconate. The two series were similar enough for purposes of comparison (Table III).

TABLE III

*Patients Receiving either a Placebo or Acetyl Choline, Showing that the Two Groups are Roughly Comparable and Showing the Incidence of Improvement Following a Course of Injections of either Acetyl Choline or a Placebo*

	Placebo (11 Patients)	Acetyl Choline (13 Patients)
Average age .. .. .	33 years	34 years
Average number injections ..	19.5	17
Male/Female ratio .. .. .	3 M : 8 F	3 M : 10 F
Diagnosis:		
Depressive reaction .. .. .	6	11
Phobic } reaction .. .. .	3	1
Obsessive }		
Anxiety reaction .. .. .	1	1
Hysterical reaction .. .. .	1	—
Average duration of illness ..	3 years	4 years
Incidence of improvement:		
Patient's assessment .. .. .	9/11	9/13
Doctor's assessment .. .. .	9/11	7/13

The results of treatment were assessed both by the patient and the referring doctor. Nine of the 11 patients receiving calcium gluconate were improved (82 per cent.). Slightly lower figures were obtained for the patients receiving acetyl choline, the referring doctor's assessment being 7 improved out of 13 (54 per cent.) and the patients' own assessment for improvement being 9 out of 13 (69 per cent.).

#### DISCUSSION

It is well known that there is a tendency for improvement to occur in two-thirds of patients with psychoneurotic disorders, and although over 50 per cent. of our 110 patients improved with acetyl choline, control studies with calcium gluconate showed that this was not due to any specific effect of the drug. These results confirm the previous report by Hawkings and Tibbetts (1956), who also found improvement to occur in 50–60 per cent. of patients whether they were given acetyl choline or sterile water. In view of these results the improvement rate of 70 per cent. for the most favourable type of case, as reported by Phillips and Hutchinson (1954), cannot be attributed to a specific effect of acetyl choline.

This conclusion cannot be wholly unexpected, as acetyl choline is rapidly destroyed in the blood, and it is doubtful if, after intravenous injection into the arm, it has any direct action on the brain. Electrical changes in the brain certainly occur after rapid intravenous injection of acetyl choline, but many of these changes are attributable to anoxia (Williams, 1941; Phillips *et al.*, 1952). Other workers are convinced that the pronounced cardiovascular upset following such a rapid injection are responsible for all the changes in the EEG picture (Harris and Pacella, 1943; Ajmone-Marsen and Fuortes, 1949). Masciocchi

(1953) believes that intravenous acetyl choline has a direct effect on the brain, but the changes in the EEG tracings which he uses to illustrate his point are almost certainly muscular in origin.

#### SUMMARY

1. One hundred and ten patients have been given acetyl choline treatment for mild psychiatric disorders. An estimated 53 per cent. had subjective improvement of their symptoms.

2. A control study of 13 patients receiving acetyl choline and 11 patients receiving calcium gluconate showed no significant difference in the incidence of improvement between the two groups.

3. It was concluded that acetyl choline has no specific therapeutic effect in the treatment of mild psychiatric disorders.

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