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Combined Chlorpromazine and Electroconvulsive Therapy in Mania

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We report the efficacy of combined chlorpromazine and electroconvulsive therapy (ECT) in the treatment of mania. Two groups of 15 manic patients received eight ECT sessions either actual or simulated, in a double-blind, controlled study. All patients also received 600 mg of chlorpromazine daily until the sixth session. Results indicate that the group receiving the combination of chlorpromazine and ECT did significantly better than the other group.

Published reports on the use of electroconvulsive therapy (ECT) in mania are not common, despite more than half a century of use. There were contradictory reports of its efficacy before pharmacotherapy began to be used. Although some psychiatrists judged ECT to be as effective for mania as it was for depression (Impastato & Almansi, 1942; Kalinowsky, 1943) others considered it to be less so (Smith *et al*, 1941, 1943). Early investigators also felt that manic patients required more frequent therapy, usually multiple, daily treatment at the beginning of the course, and that a larger course of treatment was needed compared with that required by most depressed patients (Kalinowsky, 1943; Thorpe, 1947). It should be noted, however, that opinions about clinical improvement published during this period were mostly anecdotal. Later, there was also some debate about whether manic patients treated with ECT were more vulnerable to relapse, early recurrence or were prone to rapid cycling in bipolar illness (Kukopuolous *et al*, 1983).

Several retrospective studies evaluating the efficacy of ECT in mania have been reported (McCabe, 1976; McCabe & Norris, 1977; Thomas & Reddy, 1982; Black *et al*, 1987; Alexander *et al*, 1988; Stromgren, 1988; Mukherjee & Debsikdar, 1992). The cumulative data from these show that ECT was associated with recovery or marked clinical improvement in most manic patients. Two studies (Alexander *et al*, 1988; Stromgren, 1988) also showed ECT to be effective in patients with drug-resistant mania, but the limitations of these reports include retrospective design, lack of use of operationalised criteria for diagnosing mania, heterogeneity of sample, lack of use of standardised rating scales for evaluating final outcome, lack of control over medication and failure to eliminate therapist bias in selection and preference for treatment.

Contemporary treatment of manic episodes relies heavily on the use of lithium salts, neuroleptics or anticonvulsant drugs. By contrast, the role of ECT in mania has gained little attention. Data are available from only two prospective controlled studies in recent years – one in Indiana, USA (Small *et al*, 1988) and the other in New York (Mukherjee *et al*, 1988). Small *et al* (1988) compared ECT and lithium in the treatment of acute manic episodes, whereas the New York study tried to determine whether ECT was therapeutically superior to continued intensive pharmacotherapy in manic patients who had failed to show a response to lithium or a neuroleptic. Combined data from both studies showed that ECT was associated with recovery or marked clinical improvement in 30 of 39 cases.

Although conducted using comparatively sound methods, the study by Small *et al* (1988) also had some limitations. It was not completely double blind, there was a high rate of attrition, and the concomitant use of neuroleptics in variable doses in both groups could have contributed to the efficacy of treatment. The study included patients with bipolar disease presenting in manic/mixed phases. Thus the sample was not truly homogeneous and ironically, baseline ratings of depression emerged as the strongest predictor of treatment response in the management of mania. The study by Mukherjee *et al* (1988) also used sound methods but had the disadvantage that the sample size was too small to make generalisations about the results, and the criteria for inclusion in the study appeared to be biased towards non-response.

As the use of antipsychotic drugs has become widespread, to combine such drugs with ECT has also become common practice. This treatment modality has been the focus of research in psychotic disorders, especially schizophrenia (Taylor & Fleminger, 1980; Janakiramaiah *et al*, 1982; Brandon *et al*, 1985; Abraham & Kulhara, 1987) but has not been reported as frequently in manic disorder. In a developing country such as India, there have been few studies.

We therefore conducted a prospective, double-blind, controlled study, using standardised rating instruments, to overcome the pitfalls of previous reports, to evaluate the role of ECT combined with chlorpromazine in mania.

Method

Manic patients attending the psychiatry out-patients department or admitted to the psychiatry ward of our institute were recruited. The criteria to be satisfied were:

(a) fulfilment of DSM-III-R (American Psychiatric Association, 1987) diagnostic criteria for a manic episode.
(b) an age of onset of the first episode of between 20 and 40 years.
(c) a minimum score of 14 on the Mania Rating Scale (MRS) (Bech *et al*, 1979)
(d) no lithium or any other prophylactic treatment
(e) no ECT in the last six months.

The sample consisted of an experimental group and a control group, both of 15 patients independently diagnosed to have mania by two investigators (PK and AA). The experimental group consisted of patients who received eight bilateral, modified ECT sessions and a fixed daily dose of 600 mg of chlorpromazine until six sessions had been given. After the sixth session, the dose of chlorpromazine was either modified or chlorpromazine was replaced by another neuroleptic according to the necessity of each patient. The control group consisted of patients who received eight simulated ECT sessions and the same dose and schedule of neuroleptic drugs as the patients in the experimental group.

At intake, one of the investigators (SS) recorded sociodemographic and clinical profiles by interviewing patients and their relatives. The same investigator also rated the patients on MRS (Bech *et al*, 1979) and the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962). The method and course of treatment were explained to patients and their relatives and consent was obtained for both ECT and anaesthesia. The patients were then randomly allocated (by PK) to one of the two treatment groups. The other investigators, the patients and their relatives were blind to this allocation.

Anaesthesia was given by thiopentone sodium (150–300 mg), and scoline (25–30 mg) was used as a muscle relaxant. All patients were premedicated with atropine. Modified ECT at 110 V for 0.6 s using bilateral fronto-temporal leads and sinusoidal current, was given to the ECT group three times per week. The cuff method was used to ensure that patients had genuine seizures.

Patients in the simulated ECT group were similarly anaesthetised and electrodes were placed on the forehead but no electric shock was administered. It must be emphasised that the team administering ECT was in no way involved in patient selection or subsequent evaluations.

One of the investigators (SS) interviewed each patient and their relatives before each block of two actual or simulated ECTs, that is, before the third, fifth and seventh sessions, and finally, at least 24 hours after the eighth session between 0800 and 0900 h. Following the interview, all patients were rated again on MRS and BPRS. Any extra medication used was also noted. Anticholinergic agents for extrapyramidal symptoms, nitrazepam for night sedation and intravenous diazepam to control acute excitement were used whenever necessary.

Patients whose scores fell below 6 on MRS and remained so for at least one week after completion of eight actual or simulated sessions were considered to have recovered and took no further part in the study. For those who did not recover, a follow-up assessment was done every two weeks in the first month and every four weeks in the next two months. During this period, patients were maintained on neuroleptics and other necessary drugs and were carefully monitored. At every follow-up, patients were rated on MRS and BPRS, and those whose scores fell below 6 on MRS and thus maintained for at least one week were considered to have recovered and consequently took no further part in the study.

Parametric variables were analysed by coefficients of correlation, unpaired t tests and repeat measure analyses of variance (ANOVA). Non-parametric variables were analysed by χ^2 tests and Fisher's exact probability tests.

Patients whose symptoms were not controlled by the treatment strategy were dropped from the study.

Results

A total of 32 patients satisfying the criteria were included in the study between 1 July 1990 and 30 June 1992. Two patients in the simulated ECT group left the study, because of a deterioration in their clinical condition, leaving a final sample of 30.

The two groups did not differ significantly in any of the sociodemographic variables (age, sex, marital status, occupation, education, religion, family type or place of residence) or any clinical variables (family history of mental illness, past history of affective disorder, mean duration of index episode before intake into the study and severity of the index episode as rated on MRS and BPRS). In the total sample of 30 patients, however, it was found that those who had a family history and past history of affective disorder had a more severe manic episode at index evaluation than those who did not have positive histories.

At the end of eight sessions, although 12 patients in the ECT group had made a complete recovery, in the simulated ECT group only one had recovered.

When serial scores of patients in both groups were analysed on repeat measure ANOVAs, the results showed that there was a significant main affect for group (F 1,28 = 18.59, $P<0.001$) indicating that overall, at the four points of assessment, scores in the ECT group were significantly less than scores in the simulated ECT group.

There was a significant main effect for time (F 4,112 = 218.19, $P<0.0011$) indicating that both groups improved significantly across time; Scheffe's multiple comparison test revealed that significant improvement was observed from the first rating after the baseline assessment, that is, after the second session.

Table 1
Mania Rating Scale scores in the study groups during treatment

Time of evaluation	ECT ($n=15$)		Simulated ($n=15$)	
	Mean	s.d.	Mean	s.d.
At intake	25.53	3.88	23.46	1.59
After 2nd ECT	18.80	4.21	21.08	1.48
After 4th ECT	13.08	4.77	19.46	1.50
After 6th ECT	6.93	5.15	18.73	2.46
After 8th ECT	4.6	4.91	12.13	4.18

Repeat measure ANOVA
Significant main effect for group: F 1,28 = 18.59, $P<0.001$.
Significant main effect for time: F 4,112 = 218.19, $P<0.001$.
Significant time and group interaction: F 4,112 + 29.6, $P<0.001$.

There was a significant group and time interaction (F 4,112 = 29.6, $P<0.001$) indicating that the ECT group improved at a significantly faster rate than the simulated ECT group; this difference in the rate of improvement was also observed after the second session (Scheffe's test). Details of serial scores on MRS are given in Table 1.

Although both groups were matched on overall severity of mania (as rated on MRS), at the time of intake, patients in the ECT group had significantly higher scores on four items, namely verbal and motor activity, mood and sleep disturbance. At the end of six actual or simulated sessions, that is, until the drug doses were held constant, the scores on all four items, along with four others i.e. hostility, self-esteem, conduct and work, had significantly reduced in the ECT group compared with the simulated ECT group.

Only three patients in the ECT group did not recover completely by the end of eight sessions. These three patients did not differ significantly on any sociodemographic or clinical variables compared with the rest of the patients in the group. The average chlorpromazine equivalent dose per patient until recovery was 718 mg per day.

In the simulated ECT group, of the 14 patients who were followed up after the completion of eight simulated sessions, six recovered completely after two weeks, another six after four weeks and the remaining two after eight weeks. All patients required an increase in the dose of neuroleptics to achieve clinical recovery. In this group, the average daily chlorpromazine equivalent dose was 1171 mg.

Significantly more patients (11) in the simulated ECT group required an increase in antipsychotic medication compared with the ECT group (two patients) ($P<0.05$, Fisher's exact probability test).

The mean duration of the index episode of mania following initiation of treatment in the ECT group was 20.6 days. When data were analysed for those patients who recovered completely after eight sessions, the mean duration was reduced to 15 days. The mean duration of the index episode of mania in the simulated ECT group was 39.5 days. Comparison showed that patients in the ECT group had a significantly shorter duration of mania ($t=3.46$, $P<0.001$) than patients who received simulated ECT.

No significant relationship was found between any of the sociodemographic variables and improvement of mania with ECT. Among the clinical variables, only high scores on disturbance of sleep and disruption of work (on MRS) were found to be significantly associated with improvement at the end of treatment with ECT.

Discussion

Our study demonstrated that, in the two groups of manic patients comparable for age, sex, duration and severity of illness, the group receiving the ECT–chlorpromazine combination showed significantly greater and faster improvement than the simulated ECT–chlorpromazine group, although patients in both groups improved significantly over the study period. This finding is contrary to the report of a bimodal effect of ECT on drug-resistant manic patients by Mukherjee *et al* (1988). The difference could be explained by the different selection criteria of the two studies.

This improvement was noticed from the second session. Although almost half the patients recovered completely after six sessions, most had recovered fully after eight. A reasonable conclusion is therefore that a minimum of six to eight sessions on alternate days are required for the control of acute manic excitement in combination with a moderate dose of neuroleptics. This finding is contrary to earlier reports stating that, initially, manic patients require an intensive course of ECT to control their symptoms (Smith *et al*, 1943; Kemp, 1945; Kino & Thorpe, 1946). Our findings also refute claims that manic patients require a prolonged course of ECT before they achieve therapeutic remission (Kalinowsky, 1943; Thorpe, 1947). It should be recognised that before 1954 this study would not have been possible. Nonetheless, Smith *et al* (1967) showed beneficial results by treating 'schizophrenic' patients with an ECT/drug combination, when compared with drugs alone. Although they diagnosed the patients as having 'schizophrenia', it is conceivable that the distinction between bipolar disorder with psychosis and schizophrenia with excitement was not made at that time, and the patients described were probably suffering from 'mania'. Their findings are consistent, however, with contemporary results of both retrospective and prospective studies of ECT in mania, discussed above.

When individual manic symptoms were considered in our study, it was noted that ECT had a substantial ameliorative effect on all the manic symptoms (recorded on MRS). Moreover, the fact that none of the patients in either group had depression also emphasises the homogeneity of the sample. The results of this study can, therefore, be generalised to any population of manic patients. This is of

considerable importance compared with the results of Small *et al* (1988).

Another important finding is that the number of patients in the ECT group who required additional medication, both of dose and duration, is significantly fewer than in the simulated ECT group. Distressing side-effects such as extrapyramidal symptoms are one of the major limitations of intensive neuroleptic therapy. Our findings indicate that at least for short-term remission of manic episodes, the risk of such side-effects can be minimised by combining ECT with a moderate dose of neuroleptic.

It is generally accepted that manic patients show poor drug compliance and do not adhere to a fixed treatment schedule. This was a major drawback in the study by Small *et al* (1988). In the present study, however, the drop-out rate was very low (2 of 32), adding to the validity of the results.

Our findings demonstrate that a combination of ECT and a moderate dose of a neuroleptic is extremely effective in rapidly aborting an acute episode of mania. This shortens the hospital stay and is thus cost-effective. These considerations are important in India, where health resources are scarce. This finding is also compatible with other studies conducted in a similar way on schizophrenia, where it has been shown that combined ECT and neuroleptic therapy enhance the rate of improvement over either treatment alone (Taylor & Fleminger, 1980; Brandon *et al*, 1985; Abraham & Kulhara, 1987). Empirically, ECT in mania is generally recommended either when the illness is very severe or is resistant to an intensive course of pharmacotherapy. Our results highlight the fact that ECT can be recommended for any manic patient, irrespective of the severity or the duration of the illness.

Mechanism

A possible mechanism for the efficacy of the drug–ECT combination compared with drugs alone could be as a result of the changes in the blood–brain barrier after ECT. Bolwig (1984, 1988) has shown that, although there is no real breach in the blood–brain barrier, there is evidence of increased transport of blood-borne chemicals across the capillary membranes during and after ECT. It can be argued therefore that patients in the ECT group had more chlorpromazine available to their central nervous systems than those who had simulated ECT, resulting in a more rapid recovery. Similar findings have been documented in recent studies with schizophrenic subjects (Friedel, 1986; Gujaverty *et al*, 1987). Unlike schizophrenia, however, dopamine is not as strongly implicated in the aetiopathogenesis of mania, and higher concentrations of antipsychotics in the CNS may not be responsible for the efficacy of the combined treatment regimen.

There is also some evidence that the antimanic effect of ECT is related to its anticonvulsant/inhibitory action on the brain (Mukherjee, 1989) and neuroleptics, through their potential to reduce the seizure threshold, would appear to antagonise such actions. This suggests new areas of research into the mechanism of action of ECT in mania, either alone or in conjunction with neuroleptics.

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