

PREDICTORS OF RESPONSE TO ELECTRO-CONVULSIVE THERAPY IN MAJOR DEPRESSION

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ABSTRACT

This study analyses the predictors of response to electro-convulsive therapy in major depression. The significance of the initial response to ECT as a predictor of outcome was also studied. 30 patients who met the diagnostic criteria for major depression, single episode, as defined by DSM-III-R were treated with 6-10 ECT sessions. Patients who had shown overall improvement by 50% or more on the Hamilton Depression Rating Scale (HDRS) were considered responders. 19 (63.33%) patients were responders while 11 (36.67%) patients were non-responders. These two groups differed significantly with regard to presence/absence of a delusion, diurnal variation of mood, and baseline HDRS score for hypochondriasis. Early improvement in depression was found to have a positive correlation with overall improvement in depression after the full course of ECT. Multiple linear regression analysis showed that approximately 56% of variability in outcome could be explained by the variables hypochondriasis, delusion and diurnal variation of mood taken together. A logistic regression model based on these 3 variables classified 83.3% of the patients correctly. The implications of these findings are discussed.

Key words: Depression, electro-convulsive therapy, predictors of response

Since the time of introduction of ECT, there has been a need to define a precise method of determining whether a particular depressed patient will respond to ECT. In spite of efforts to identify the predictors of response to ECT, there still remains significant uncertainty. Data generated through decades of research in this area appears to be inconclusive.

The significance of the endogenous/reactive syndrome-dichotomy with regard to response to ECT has intrigued researchers for many decades. One of the earliest studies (Thomas, 1954) observed that reactive depression did not do well with ECT. Subsequently, Carney et al (1965), Fink (1982) and Andrade et al (1989) observed that endogenous symptoms were predictors of a favourable response. This view had not been supported by Mendels (1965) who, in addition,

observed that majority of cases present a mixed "endo-reactive" picture. The association between delusions and good treatment response to ECT has been observed by Kantor & Glassman (1977), Crow et al (1984) and Black et al (1987). Hickie et al (1996) observed that the combination of marked psychomotor change and psychotic features predicted the best response to ECT. However, Sobin et al (1996) has advocated ECT as a viable treatment option for patients with major depression regardless of the presence or absence of psychosis, retardation and/or agitation. There also appears to be a correlation between HDRS scores and response to ECT (Pande et al: 1968) though this aspect has not received focus in later studies, and merits further research. Wilkinson et al (1993) demonstrated a clear positive correlation between increasing age and response to ECT. In contrast to the

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findings mentioned above, one study (Abrams, 1973) found that none out of 22 various clinical features were significantly associated with outcome.

The significance of anti-depressant effect early in a course of ECT with regard to prediction of response to ECT has also received some attention from researchers. Scott & Whalley (1993) had reviewed various reports in this area and concluded that there is considerable controversy regarding this issue. A close correlation between the degree of improvement over the initial ECT sessions and the improvement over the whole course of treatment has been noted by Rodger et al. (1994) and Gupta et al. (1998).

Analysis of important methodological issues in the studies of predictors of response to ECT in depression shows that, often, a meaningful comparative study cannot be made of the observations noted by different research groups. Prien et al. (1991) demonstrated inconsistency in the labelling and definition of change-point/response to treatment across various studies. Diverse definitions of satisfactory response to ECT have been utilised by various researchers: 50% reduction in total HDRS score (Mendels, 1967), $\geq 75\%$ reduction in initial HDRS score (Andrade et al., 1988), 60% reduction in total HDRS score (Gupta et al., 1998). Nierenberg and Amsterdam (1990) have reported that the most widely used definition of full response in the psychiatric literature is a 50% decrease in HDRS score. Review of literature also reveals absence of uniformity in the diagnostic criteria for depression used in past research. Moreover, many earlier studies have not stated the specific diagnostic criteria employed in the patient selection process, which may be considered a methodological weakness. As a result of all these issues, considerable ambiguity still pervades the clinical prediction of response to ECT in major depression in spite of extensive research over many years. This study has been undertaken with the following objectives: (1) to study the various clinical

predictors of response to ECT in patients with major depression, and (2) to study the significance of the initial response to ECT as a predictor of outcome in patients with major depression.

MATERIAL AND METHOD

This study was conducted in the department of Psychiatry at the Jawaharlal Institute of Post-graduate Medical Education & Research (JIPMER), Pondicherry, over a period of 18 months. The study sample consisted of 30 patients who met the diagnostic criteria for Major Depression, single episode, as defined by DSM-III-R (APA, 1987), and had no other comorbid psychiatric disorder or past history of affective episode or any other psychiatric illness. Patients who had already received psychotropic medication or ECT for the depressive episode were not included. This study, which has a prospective design, was conducted entirely in an inpatient setting.

Following informed consent, each patient was evaluated using a semi-structured proforma that elicited basic sociodemographic details and the clinical features in detail. Each patient was rated on the 17-item Hamilton Depression Rating Scale (HDRS). The treatment regimen consisted of 2 sessions of modified ECT per week. All psychotropic medications were excluded from the treatment regimen. Anaesthesia for ECT was induced with Thiopental (2-3 mg/kg I.V.) and muscle relaxation achieved using Succinylcholine (0.5-1.0 mg/kg I.V.). The ECT device used was of the brief-pulse, constant current type. Bilateral electrode placement was employed, with electrical stimulus dosage ranging from 60 mC to 180 mC. Seizure duration was measured using the cuff method and a minimum seizure duration of 25 seconds was ensured. Each patient was rated on HDRS after every 2 sessions of ECT, i.e., once every week. The ECT course was discontinued when the patient showed no further reduction in HDRS scores over 2 successive

treatments, after a minimum of 6 ECTs. The total number of ECT sessions ranged between 6 and 10. On completion of the ECT course, patients were again rated on HDRS in order to assess overall improvement. HDRS ratings were all done in the forenoon, for all patients, by a consultant psychiatrist (R.C.). Patients who had shown overall improvement by 50% or more on the HDRS were considered as responders, whereas, patients who had shown no improvement or had improved only by less than 50% on the HDRS were considered as non-responders.

The variables included for analysis in this study include various clinical features, scores on various HDRS items, age of patient, baseline HDRS score, first week HDRS score, and percentage change from baseline HDRS score after 2 ECT sessions. Preliminary statistical methods employed include chi-squared test, t-test and correlation analysis. In order to check if any of the variables could reliably be used to predict outcome of depression treated with ECT, regression analysis was employed. The outcome variable in this case can be expressed both as a numerical continuous variable (percentage of change from baseline score) and as a categorical variable (responder/non-responder). This necessitated the use of multiple linear regression and logistic regression, respectively.

RESULTS

A total of 42 patients had been screened, of which 37 patients fulfilled the proposed inclusion criteria. Of these, consent for ECT could not be obtained in 2 cases and 3 other patients were not willing to get admitted into the ward. 2 patients did not receive the minimum required number of at least 6 ECT sessions and therefore had to be excluded from this study. A total of 30 patients completed the treatment protocol successfully. The sample consisted of 30 patients [13 (43.33%) male patients and 17(56.67%) female patients]. Age ranged from 14 years to 60 years, with a mean of 33.07 years (S.D = 9.6). 5 (16.67%) patients were single, 23

(76.67%) patients were married and 2 (6.67%) patients were widowed. Onset of illness was insidious in 21 (70%) patients and acute in 9 (30%) patients. A precipitating factor could be identified only in 8 (26.67%) patients. 5(16.67%) patients had a positive family history of affective illness. DSM-III-R melancholic features were present in 20 patients, while psychotic features were observed in 12 patients. 19 (63.33%) patients responded favourably to ECT while 11 (36.67%) patients were non-responders. Baseline mean total HDRS scores and the final mean total HDRS scores were 28.1(S.D=5.1) and 7.9 (S.D=1.6) respectively, in the group of responders, and 27.3 (S.D=4.0) and 18.4 (S.D= 5.1) respectively, in the non-responders.

Responders and non-responders were compared based on their sociodemographic and clinical profile. Significance level was set at $p < 0.05$. The two groups differed significantly with regard to delusion and diurnal variation of mood (table 1) and baseline HDRS score for hypochondriasis (table 2). The two groups did

TABLE 1
COMPARISON OF RESPONDERS AND NONRESPONDERS WITH REGARD TO CLINICAL PROFILE

Variable	Test	p-value
1. Sex	FET	0.454
2. Marital status	CST (pearson)	0.330
3. Type of onset	FET	0.100
4. Duration (< or > one year)	FET	0.126
5. Precipitating factor	FET	0.672
6. Family history	FET	0.626
7. Anhedonia ^(a)	--	--
8. Loss of emotional reactivity	FET	0.417
9. Diurnal variation of mood	FET	0.023*
10. Early morning awakening	CST+YCC	0.130
11. Feeling of worthlessness	FET	0.100
12. Impairment of concentration	CST+YCC	1.000
13. Delusion	FET	0.0006***
14. Hallucination	FET	1.000

Note (a) Code - CST=X² test, YCC=Yates continuity correction
FET=Fisher's exact test

(b) d.f.=1 for all variables except marital status (d.f.=2)

(c) Significance . * = Probably statistically significant
(0.01 < p < 0.05)

** = Statistically significant (p < 0.01)

*** = Highly statistically significant (p < 0.001)

(d) The variable "anhedonia" could not be analysed since all patients in the sample had this symptom.

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TABLE 2
COMPARISON OF RESPONDERS AND NONRESPONDERS WITH REGARD
TO BASELINE HDRS ITEM-SCORES

Variable	Baseline mean HDRS score		t-test		
	Responders	Non-responders	t-value	d.f.	p
1. Depressed mood	3.7±0.6	3.5±0.7	0.97	28	0.338
2. Suicidal impulses	2.4±1.3	1.7±1.3	1.26	28	0.218
3. Guilt feelings	1.4±1.0	0.7±1.1	1.75	28	0.092
4. Fatigability	2.1±0.8	2.2±0.6	0.44	28	0.661
5. Anxiety	1.7±1.4	1.5±1.0	0.28	28	0.779
6. Hypochondriasis	0.8±0.8	1.5±0.8	2.20	28	0.037*
7. Obsessions	0.1±0.2	0.0±0.0	0.76	28	0.456
8. Loss of insight	1.4±1.5	0.8±0.9	1.41	27.93	0.169
9. Retardation/agitation	2.7±1.0	2.5±1.1	0.71	28	0.481
10. Sexual interests	1.3±0.8	1.7±0.5	1.64	28	0.112
11. Weight loss	0.9±0.7	0.8±1.0	0.22	16.62	0.825

Note: Significance: * = Probably statistically significant (0.01 < p < 0.05)

TABLE 3
COMPARISON OF RESPONDERS AND NONRESPONDERS WITH REGARD
TO TOTAL HDRS SCORES

Variable	Responders	Non-responders	t-value	t-test d.f.	p
1. Baseline total HDRS score	28.1±5.1	27.3±4.0	0.46	28	0.646
1st week total HDRS score (after 2 ECTs)	21.7±3.8	22.8±4.1	0.58	28	0.815
% reduction in HDRS score after 2 ECTs	22.2±14.8	16.2±10.3	1.20	28	0.238

Note: p > 0.05 not statistically significant

TABLE 4
MULTIPLE REGRESSION ANALYSIS OF
HYPOCHONDRIASIS, DELUSION AND DIURNAL
VARIATION OF MOOD VS. OUTCOME

	B	SE(B)	Beta	p
Hypochondriasis	-3.488	3.862	-0.138	0.375
Delusion	-20.954	6.804	-0.487	0.005
Diurnal var. of mood	-13.784	6.148	-0.315	0.034
Constant	116.679	11.578	--	0.000

Multiple R=0.749, R square=0.562, adjusted R square=0.517, standard error=15.003

not differ significantly with regard to baseline total HDRS score and % change in total HDRS score over one week (table 3). Correlation analysis demonstrated that the degree of hypochondriasis (baseline HDRS score) had a negative correlation with the overall percentage change in total HDRS score ($r=-0.4793$, $p=0.007$). The

amount of change in the total HDRS score in the 1st week (early improvement) was positively correlated with the overall total percentage change in total HDRS score ($r=0.4494$, $p=0.013$).

Regression analysis was employed to test the predictor status of the variables that had been demonstrated, through preliminary statistical analysis, to be significantly correlated with outcome of depression. Simple linear regression analysis showed that approximately 20% of variation in overall improvement could possibly be predicted by improvement over the first week (R square=0.20194). Multiple linear regression analysis (table 4) revealed that approximately 56% of variability in outcome could be explained by the variables hypochondriasis, delusion and diurnal variation of mood taken together. These three variables were then subjected to logistic

TABLE 5
LOGISTIC REGRESSION ANALYSIS OF HYPOCHONDRIASIS, DELUSION AND DIURNAL
VARIATION OF MOOD VS. OUTCOME

	B	SE(B)	Wald	d.f	p	R	Exp(B)
Hypochondriasis	0.226	0.695	0.106	1	0.745	0.000	1.254
Delusion	-5.064	22.343	0.051	1	0.821	0.000	0.006
Diurnal var of mood	-0.995	0.651	2.334	1	0.127	-0.092	0.370
Constant	-5.459	22.357	0.060	1	0.807	---	

regression analysis (table 5). 15 patients who were responders were correctly predicted by the logistic regression model to be responders. Similarly, 10 patients who were non-responders were correctly predicted to be non-responders. Overall, 83.33% of the 30 patients were correctly classified.

DISCUSSION

This study attempts to identify the predictive capabilities of various clinical variables in patients of major depression, with regard to outcome following ECT. The sample consisted of 30 patients who met the diagnostic criteria for major depression, single episode, as defined by DSM-III-R (APA, 1987). Since the most widely used definition of response in the psychiatric literature is a 50% decrease in HDRS score (Nierenberg & Amsterdam, 1990), the same was adopted in this study too, to enhance comparability with other similar studies. The results of this study are largely based on the powerful statistical methods of linear and logistic regression analysis. It is a well-known fact that regression analysis is a more useful method than simple correlation with regard to prediction of one variable based on another.

Before we attempt to draw inferences from our observations, certain limitations of this study need to be discussed. The sample size of n=30 is relatively small, which affects the power of the statistical tools employed. Further, our study sample consisted predominantly of patients from a lower socio-economic background, and therefore is not very representative. Another issue that deserves mention is the importance of biological predictors

of response to ECT in depression. Though earlier studies have thrown light upon this issue, the same could not be studied in this project, due to various practical limitations.

Age did not show any significant correlation with outcome in this study, which is in agreement with the observation made by Ottoson (1962) and Andrade *et al.* (1989). Our finding does not concur with that of Black *et al.* (1987) and Wilkinson *et al.* (1993), who noted specifically that older patients of major depression respond better, when treated with ECT. Type of onset of illness, duration of illness, presence of precipitating factor and family history of affective illness were observed to have no significant association with outcome in this study. These findings are supported by studies conducted by Ottoson (1962), Abrams *et al.* (1973) and Pande *et al.* (1988). In contrast to this, Mendels (1965) had concluded that precipitating factors were associated with a poor response to ECT while Hobson (1953) had observed that sudden onset and duration of illness of less than one year were correlated significantly with a good response to ECT.

On analysing the melancholic group of symptoms, only diurnal variation of mood appeared to be significantly different in its distribution among responders and non-responders. Other studies have not made any specific mention regarding diurnal variation of mood. Mendels (1965) observed that none of the clinical factors that one used to define endogenous depression were associated with response to ECT when these factors were studied individually, whereas Nystrom (1964) had reported that early morning waking and retardation carried good prognostic significance

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with regard to response to ECT. Fink (1982) and Abhyankar (1985) had concluded that patients with a syndrome of melancholia have the best prognosis for short-term outcome with ECT. Pande et al. (1988) reported that, while agitation was significantly more frequent in the poor responders, retardation, endogeneity and loss of reactivity were not significantly different between the two groups. Hickie et al. (1996) have noted that the combination of marked psychomotor change and psychotic features predicted the best response to ECT, though psychomotor retardation/agitation was not found to have any significant association with outcome in our study. Crow et al. (1984) had reported that features of endogenous depression did not, in themselves, appear to predict response to ECT.

In this study, presence/absence of a delusion was associated with a good response to ECT. Similar observations have been made by Mendels (1965), Crow et al. (1984), Fink (1982) and Black et al. (1987). The present study did not find the responders and non-responders to be significantly different in terms of loss of insight. Earlier studies have reported conflicting results in this regard. Abrams et al (1973) did not find loss of insight to be associated with outcome. This is contradictory to the earlier observation of Hobson (1953) that good insight is a favourable feature that is correlated significantly with outcome. In this study, baseline HDRS score for hypochondriasis was observed to be significantly associated with outcome. A similar observation had been made by Hobson (1953). While anxiety was not found to be significant in our study, somatic anxiety was found by Pande et al (1988) to be significantly higher in the poor responders.

The results of the present study suggest that the baseline severity of depressed mood and suicidal impulse on HDRS have no significant association with outcome. The symptom of a feeling of worthlessness seemed to approach but did not reach statistical significance. Nystrom (1964) had observed that profound depression in mood was correlated

significantly with good outcome. Fink (1982) and Abhyankar (1985) noted that patients who are severely ill have the best prognosis with ECT. Andrade et al (1989) showed that lesser initial severity of depression was associated with good response, which is in contrast to the first three studies. Baseline mean total HDRS score was not found to be significantly different in the responders and the non-responders in our study. Pande et al (1988) had stated that, their study showed that patients with higher initial total HDRS score did less well with ECT. Since ECT has traditionally been advocated for patients with severe depression, this aspect definitely merits further research with a large sample population.

This study found that the amount of change in total HDRS score in the first week (i.e., after two ECT sessions) was positively correlated with the overall total percentage change in total HDRS score (i.e., after the full ECT course). Simple linear regression analysis had shown that, approximately only 20% of variation in overall improvement could possibly be explained by improvement in the first week. However, there appears to be considerable controversy about the significance of any anti-depressant effect early in a course of ECT, as stated by Scott and Whalley (1993). Rodger et al (1994) had observed that there was a close correlation between the degree of improvement over the first three treatments and the degree of improvement over a whole course of ECT. The finding in this study is also supported by the observations made by Andrade et al (1989) and Gupta et al (1998) that response to first ECT could be taken as predictor of response in depression.

To conclude, it would be appropriate to draw some inferences based on the present study. Presence of a delusion in patients of major depression appears to have a strong association with favourable outcome when treated with ECT. Presence of diurnal variation of mood in patients of major depression appears to have some association with favourable outcome when treated with ECT. The more the hypochondriacal

symptoms a patient of major depression has, the lesser is the improvement brought about by ECT. Predictive capability of the three variables, namely, delusion, diurnal variation of mood and hypochondriasis in relation to response to ECT still remains uncertain and needs further research. Though early improvement in depression treated with ECT has a significant positive correlation with the overall improvement that would occur after the full course of ECT, its predictive power appears to be weak. It is imperative that further research projects are undertaken in order to bring some clarity to the ambiguous issues surrounding prediction of response to ECT in major depression.

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