

## BRIEF COMMUNICATION

# Relative impact of diagnosis and clinical stage on response to electroconvulsive therapy: a retrospective cohort

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**Objectives:** Electroconvulsive therapy (ECT) is commonly indicated for refractory psychiatric disorders. However, little research has compared response across diagnoses. Here, we aimed to evaluate the relative impact of diagnosis and clinical staging as response predictors in a cross-diagnostic sample.

**Methods:** In a retrospective cohort of adult inpatients (n=287) who underwent at least six sessions of ECT, we investigated predictors of complete response (a clinical global impression of 1) to ECT. We use adjusted regression models to estimate the impact of clinical diagnosis and staging on complete response and dominance analysis to assess the relative importance of these predictors.

**Results:** Those for whom a depressive episode was a primary indication for treatment were the most likely to have complete improvement, while those with psychosis were the least likely; clinical stage had a significant influence on outcome in all diagnoses. A diagnosis of psychosis was the strongest predictor of non-response.

**Conclusions:** A diagnosis of psychosis (mainly schizophrenia) was the strongest predictor of non-response. We also found that clinical staging can aggregate information on ECT response that is independent of clinical diagnosis.

**Keywords:** Staging; electroconvulsive therapy; depression; mania; psychosis

## Introduction

Electroconvulsive therapy (ECT), a generally safe and effective treatment for a host of severe refractory mental disorders, including mood and psychotic disorders, is prescribed throughout the world for these indications.<sup>1,2</sup> However, response predictors in ECT have almost exclusively been studied in patients with major depression,<sup>3</sup> among whom severe and psychotic symptoms and older age predict a better response.<sup>4</sup> In mania and schizophrenia, the literature on response predictors is particularly scant,<sup>5,6</sup> and investigated response predictors can vary from those studied in major depression. Furthermore, the dearth of studies that include other common indications, such as refractory mania and psychosis, makes it difficult to directly compare the impact and relative relevance of predictors of treatment response across diagnoses.

Staging models propose that, in at least a substantial proportion of patients, mental illness progresses from prodromal stages to late and intractable stages. Staging has been treated as both an additional dimension to

diagnosis and as a transdiagnostic concept.<sup>7,8</sup> Such models assume that staging may be a more relevant dimension for prognosis and treatment selection than extant diagnostic categories.<sup>9</sup> There is some evidence that staging has an effect on treatment outcome, mostly in mood disorders.<sup>10,11</sup> Although it is believed that ECT might be especially useful in later stages, there is little direct evidence to corroborate this belief.

In a retrospective cohort, we assessed the effectiveness of ECT across the most common diagnoses for which it is currently prescribed. We also tested the impact of staging and the relative importance of staging and diagnosis on clinical outcome, which to our knowledge has not been investigated in relation to ECT outcome.

## Methods

Every adult inpatient who underwent ECT for an acute (i.e., not maintenance) indication at the Hospital de Clínicas de Porto Alegre from January 2009 to December

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2015 was included.<sup>12</sup> Sessions are conducted three weekly. General anesthetic (thiopental, 3 mg/kg) and a muscle relaxant (succinylcholine 0.75-1 mg/kg) are routinely administered, as per institutional protocol. The standard procedure is high-potency right unilateral placement, and the titration method is used to determine the stimulus dose during the first session. From the second session onwards, the stimulus charge is set at 6 times the seizure threshold.

The medical records were inspected for the primary ICD-10 episode diagnosis for which the procedure was indicated. In this analysis, we grouped the diagnoses as depression (unipolar or bipolar), mania, psychotic disorders (schizophrenia, schizoaffective disorder, and delusional disorder), and other diagnoses (anxiety disorders, substance use disorders, organic disorders, and movement disorders) as a residual category. Using the medical records, independent raters blinded to ECT session data determined a clinical global impression (CGI) score before and immediately after the procedure. As the main outcome of interest, we characterized complete remission as a CGI score of 1. We selected the CGI due to its ease of use by experienced raters and the transdiagnostic approach employed here.<sup>13,14</sup>

Another rater further blinded to the CGI results attributed a clinical stage to each patient based on the McGorry staging method. We chose this transdiagnostic method since it allows comparisons within and between diagnostic groups.<sup>9</sup> In our sample, most patients were at a relatively late stage, and we divided the sample into three categories for analysis ( $\leq$  stage IIIB, stage IIIC, and stage IV), based both on theoretical and distribution issues (Table S1, available as online-only supplementary material).

### Statistical analysis

Models were estimated using Poisson regression with robust estimation of variance to report independent effects and confidence intervals.<sup>15</sup> The primary outcome was remission (CGI = 1). We restricted the main analyses only to patients who underwent least six sessions, although the data from all cases did not differ significantly (available upon request). The analysis was adjusted for variables expected to influence ECT response,<sup>16</sup> such as age, sex, initial CGI score, number of sessions, drugs prescribed, diagnosis resulting in ECT indication (depression, mania, psychosis, or other), and staging ( $\leq$  stage IIIB, stage IIIC and stage IV).

We use dominance analysis to report the relative importance of independent variables based on computing the reduction in prediction error associated with each independent variable in the model. We report here general dominance weight (GDW), a decomposition of the fit statistic, also known as Shapley value decomposition. We also report complete dominance regarding the two main variables of interest (diagnosis and staging); a predictor is said to completely dominate another predictor if its dominance holds across all possible subset models.<sup>17</sup> All analyses were performed in Stata 17.0.

**Table 1** Clinical characteristics of patients who received electroconvulsive therapy (n=287)

Characteristic	
Older adults	52 (18.1)
Staging	
$\leq$ stage IIIB	104 (36.2)
Stage IIIC	151 (52.6)
Stage IV	32 (11.1)
Female sex	154 (53.7)
Primary diagnosis	
Depressive episode	140 (48.8)
Psychosis	84 (29.3)
Mania	39 (13.6)
Other	24 (8.4)
Antidepressant use	98 (34.1)
Lithium	9 (3.1)
Anticonvulsant	22 (7.7)
Antipsychotic	249 (86.8)
Benzodiazepine	55 (19.2)

Data presented as n (%).

## Results

A total of 427 patients met the inclusion criteria, and 352 had sufficient information to establish a CGI score at the endpoint (82.4%); 287 patients underwent at least 6 sessions (Table 1). The median CGI was 6 (interquartile range 6-6) before ECT and 1 (interquartile range 1-2) after ECT; complete improvement was reported in 54.6% of the patients.

Those with a depressive episode as the primary indication for ECT were more likely to have complete improvement (69%) than the other groups, followed by manic episodes (51%), other (49%), and psychosis (32%). Clinical stage had a similar influence on outcome in all diagnoses, with no interactions; the full Poisson regression model results are described in Table 2. A diagnosis of psychosis was the strongest predictor of non-response (GDW = 0.05, 32% of  $R^2$ ), and stage IV was the fourth strongest (GDW = 0.01, 6.8% of  $R^2$ ) (Table 2). A diagnosis of psychosis completely dominated stage IV across all subset models.

## Discussion

Clinical diagnosis was the main predictor of response to ECT in our sample. Patients with a primary diagnosis of psychosis (mainly schizophrenia) had a lower rate of response than those with depression. That alone accounted for an average of about a third of the variance predicted by our multivariate model. Clinical stage, nevertheless, also accounted for significant independent variance, albeit always with a smaller weight than diagnosis. We know of no other studies that have evaluated clinical stage as a predictor of response in ECT.

Having clearly defined response predictors is essential for treatment selection. While most studies thus far have investigated response predictors in major depression,

**Table 2** Risk ratios for non-response and weight explained by clinical variables in multivariable model of response to electroconvulsive therapy

	Poisson regression			General dominance	
	IRR	SE	p-value	St weight (%)	Rank
Diagnosis (vs. depression)					
Psychosis	2.06	3.71	< 0.001	32.40	1st
Mania	1.67	3.51	0.015	3.83	8th
Other	1.92	4.62	0.007	3.90	7th
Number of sessions	1.04	0.01	0.007	18.33	2nd
Male sex	6.70	9.28	0.004	16.37	3rd
Staging (vs. lower than IIIC)					
Stage IIIC	1.23	1.87	0.171	1.39	10th
Stage IV	1.60	3.18	0.018	6.84	5th
Drugs					
Antidepressants	0.87	0.15	0.401	7.12	4th
Lithium	1.17	0.42	0.669	0.14	13th
Anticonvulsants	1.05	0.22	0.813	0.06	14th
Antipsychotics	1.20	0.31	0.480	2.83	9th
Benzodiazepines	0.96	0.16	0.816	0.21	12th
Older adult	1.63	0.28	0.004	5.85	6th
Initial CGI	0.89	0.08	0.198	0.75	11th

CGI = clinical global impression; IRR = incidence rate ratios; SE = standard error.

cross-diagnostic studies can point to differences as well as similarities between diagnoses. Here, we demonstrated that patients with major depression had a clearly superior response to ECT. Recently, Tor et al.<sup>18</sup> compared ECT outcomes in a sample with similar baseline diagnoses to ours, finding that clinical outcomes were also worse for patients with psychosis, albeit not significantly different from the major depression group. The differences between the two samples included generally greater clinical improvement in depression in our sample, which might have been due to our predominant use of a right unilateral brief pulse protocol, rather than the ultra-brief pulse they employed.

The mechanism by which depression would be more responsive to ECT than psychosis is unclear at this point. We adjusted our models for age, sex, and initial severity, but patients can differ in the degree of previous resistance depending on the diagnosis, which could, in principle, be responsible for the observed effects of diagnosis. We independently established a clinical stage for each patient in an attempt to predict response beyond diagnosis. While the staging effect was smaller than that of diagnosis, it was also independent of diagnosis, and we failed to demonstrate significant interactions, meaning that late stage was a predictor of poorer response across diagnoses. Most studies thus far have only demonstrated the effect of staging through indirect measures, such as the number of episodes.

Since this was not a controlled experiment, causal explanations for the associations are unwarranted; retrospective studies are inherently limited because their data were collected for purposes other than research. We collected all data from patient records, but augmented them with measures of clinical response and staging in an

effort to obtain better information. We also thought it reasonable to obtain symptom measures from two time points, although more granular data might further discriminate outcomes. It is unclear whether the sample size was large enough to demonstrate significant differences, especially in interactions between less prevalent diagnoses, although most predictors followed similar patterns to previous studies. The lack of a control group consisting of patients treated without ECT means that we do not know whether the poorer response in the late-stage and psychosis groups would be higher than similar inpatients treated with medication. Moreover, this report is from a single center with consistent and stable use of ECT, mostly right unilateral ECT; generalizing the results to other centers that use different clinical strategies is unwarranted.

In this study we compared diagnoses for which ECT is commonly prescribed and found some relevant differences. Psychosis, as opposed to depression, had the largest negative impact on response. Moreover, the impact of clinical staging on predicting clinical improvement was also above and beyond that of diagnosis.

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## Disclosure

The authors report no conflicts of interest.

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