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'Rapid speed of response to ECT in bipolar depression: A chart review☆

K.W.F. Scheepstra [a,b,*,1], J.B. van Doorn [c,1], D.S. Scheepens [a], A. de Haan [a], N. Schukking [a], J. B. Zantvoord [a], A. Lok [a]

[a] Department of Psychiatry, Amsterdam UMC, Location AMC, University of Amsterdam, Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands
[b] Neuroimmunology Research Group, Netherlands Institute for Neuroscience, Meibergdreef 47, 1105, BA, Amsterdam, the Netherlands
[c] Department of Psychological Methods, University of Amsterdam, Valckenierstraat 59, 1018, XA, Amsterdam, the Netherlands

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ABSTRACT

Objective: To validate a faster speed of response to electroconvulsive therapy (ECT) for bipolar depression (BPD) compared to major depressive disorder (MDD)
Method: Retrospective chart review on an ECT cohort in an academic hospital setting. Speed of response was defined by the number of ECT treatments needed for response or remission.
Results: Sixty-four depressed patients were included, of whom 53 (MDD: 40, BPD: 13) could be analyzed. The bipolar group responded faster with a mean difference of 3.3 fewer ECT treatments to meet response criteria (MDD 10.4 vs. BPD 7.1, $p = 0.054$). When using mixed effects regression models for the response/remitter group ($n = 35$), a faster response for the bipolar group (AIC 252.83 vs 258.55, $\chi^2 = 11.72$, $p = 0.008$) was shown. Other factors, such as psychotic features or comorbidity, did not influence the speed of response.
Conclusion: This chart review of an ECT cohort in an naturalistic academic hospital setting shows an evident and clinically relevant faster speed of response in bipolar depression.

1. Introduction

Electroconvulsive therapy (ECT) is the most effective treatment used to treat severe and refractory depressive episodes. (Brus et al., 2017; Geddes et al., 2003; Kho et al., 2003) The chances of remission depend on the features of the depressive episode and co-morbidity, such as personality disorders. (Newton-Howes et al., 2014) Remission is achieved in around 50% of both major depressive disorder (MDD) and bipolar depression (BPD), and higher rates are reported for depression with psychotic features (63%–95%). (Brus et al., 2017; Dierckx, Heijnen, van den Broek and Birkenhäger, 2012; Geddes et al., 2003; Petrides et al., 2001) Besides response and remission, ECT is also associated with reduced short-term psychiatric inpatient readmissions for severe affective disorders. (Slade et al., 2017).

However, there consists a large heterogeneity in the trajectories of ECT response in different patient groups. There are no known biomarkers yet to predict response, and thus algorithms are solely based on clinical symptomatology and episode characteristics. For example, psychotic features, psychomotor retardation, older age, absence of medication resistance and a shorter episode duration are all positive predictive factors for response. (Haq et al., 2015; Heijnen, Birkenhäger, Wierdsma, & Van Den Broek, 2010; Heijnen et al., 2019; Newton-Howes et al., 2014; Van Diermen et al., 2018) Co-morbid (personality) disorders have a negative predictive value for response. (Newton-Howes et al., 2014)

Besides differences in treatment response, some patients require significantly less ECT sessions than others to achieve remission. Multiple studies have indicated that fewer ECT sessions were needed to treat bipolar depression. (Daly et al., 2001; Sienaert et al., 2009) A meta-analysis from 2012 showed that ECT is equally effective in MDD versus BPD, but indicated that there were not enough studies at that point for a conclusion on speed of response. (Dierckx et al., 2012) A more recent review from 2018 on the speed of antidepressant response, indicated a potentially brisker speed of response in BPD and that further research is needed. (Agarkar et al., 2018) A faster speed of response has implications for an earlier indication of ECT, as a rapid relief of severe

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* Corresponding author. Department of Psychiatry, Amsterdam UMC, Location AMC, University of Amsterdam, Meibergdreef 9, 1105, AZ, Amsterdam, the Netherlands.
E-mail address: k.w.scheepstra@amsterdamumc.nl (K.W.F. Scheepstra).

[1] Contributed equally.

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symptoms and potentially less cognitive side effects due to fewer treatments are preferred.

The aim of this study was to validate a faster speed of response in our academic hospital patient cohort and to explore clinical contributors for rapid response.

2. Materials and methods

2.1. Participants

The CRETECT-DAE (Chart Review on Efficacy and Tolerability of Electro Convulsion Therapy – Depressed Adults and Elderly) is a cohort of patients treated with ECT at an academic psychiatric hospital, between 2015 and 2020. All patients treated with ECT were selected automatically through the electronic patient system, after introduction in 2015.

Patients were included if they met the following inclusion criteria. They had to be between 18 and 80 years old and diagnosed with MDD or BPD according to the DSM-IV or DSM–5 criteria. They had to be treated with unilateral or bilateral ECT twice a week. A baseline measurement, the week before the start of ECT and 2 weeks after ending treatment, in the form of a HRSD-17 (Hamilton Rating Scale for Depression, 17 items, Dutch version) was available. Patients were excluded when diagnosed with catatonia, a psychotic disorder, a neurodegenerative disease or when they received ECT for another indication than depression. Patients were also excluded if they previously received ECT treatment in the current depressive episode. Other comorbid psychiatric disorders were not an exclusion criterion. Patients were also excluded if they previously received ECT treatment in the current depressive episode.

Data of enrolled patients were extracted from electronic patient records. An electronic case report form (eCRF) was conducted using Castor. Since it was a retrospective cohort study, no direct actions or additional experiments were performed on included participants. Therefore, the Medical Research Involving Human Subjects Act (WMO) does not apply to this study and was exempted by the Medical Research Ethics Committees United (MEC-U, reference number W19_136 # 19.170). Consent to use data was obtained from all participants.

2.2. Electroconvulsive therapy

All patients were treated according Dutch ECT guideline, starting with 6 unilateral treatments, regardless of diagnosis. The electrodes were placed unilaterally over the right hemisphere and switched to bifrontotemporal when patients did not respond to unilateral ECT and cognitive effects allowed a switch.".ECT was administered with a brief-pulse (0.5 ms), with the constant-current Thymatron IV system (Somatics LLC, Lake Bluff, Illinios, USA). Anesthesia was achieved with intravenous administration of etomidate (0.2 mg/kg) and muscle paralysis with succinylcholine (0.5–1.0 mg/kg). When patients used benzodiazepines, they were pre-treated with flumazenil. Lithium and anticonvulsants were tapered off before start of ECT and other concomitant medications were continued. Before the first session, the stimulus dose was determined using the dose-titration method for either unilateral- or bilateral treatment. (Sackeim et al., 2000) A stimulus dose of six times the seizure threshold was used for therapeutic stimulation. During the course of ECT, stimulus dosage settings were adjusted upward to maintain seizure duration of at least 20 s, as measured with the cuff method and on electroencephalogram (EEG). The number of ECT treatments was determined by clinical observation. At least 6 treatments were required before switching to bilateral and a minimum of 12 treatments to classify a patient as non-responder.

2.3. Treatment outcome

The Dutch version of the Hamilton Rating Scale for Depression 17 items (HRSD-17) was used to evaluate the effect of ECT treatment on the severity of the depressive symptoms. A baseline measurement was done prior to ECT start and a follow-up HRSD assessments were performed weekly during treatment. All measurements were done by trained clinicians on non-ECT days. Response was defined as $\geq$50% reduction of symptoms on the HRDS and remission was defined as a HRDS of <7, according to psychometric validation studies. (Frank et al., 1991; Zimmerman et al., 2013). Numbers of treatments to response is defined as the number of ECT treatments needed to achieve a reduction of 50% on the HRDS, compared to baseline.

2.4. Statistical analysis

In order to assess differences in speed of response between patient groups (MDD vs. BPD, and psychotic vs. not psychotic, PD vs non-PD), two mixed effects regression models were compared. Model 1 and Model 2 contained the random effect of number of ECT treatments and the fixed effect of group. Model 2 also contained the interaction effect between group and number of ECT treatments. This interaction effect models the differences between groups in the effect of the number of treatments on time, indicating a faster or slower decrease in HDRS. Corrections were made for other factors possibly confounding the interaction. Model performance was assessed by χ^2- tests and Akaike Information Criterion (AIC). These analyses were conducted in R (R Core Team, 2020). Additional models were fitted to assess the effect of number of failed trials and number of previous episode on speed of response. Additionally, Mann-Whitney U tests were conducted to test for group differences in the number of ECT treatments needed to reach response, and remission. Lastly, contingency table tests were conducted to test for group differences in the number of observed responses, and remissions. These analyses were conducted in JASP (JASP Team, 2020). Analysis code, results, and setup are available at an Open Science Framework (OSF) repository.

3. Results

3.1. Patient characteristics

Of the 106 patients treated with ECT between 2015 and 2019, 37 patients were excluded because they met one or more exclusion criteria. 11 patients dropped out because of several reasons. 40 patients with MDD and 13 patients with BPD, for a total of 53 patients were included for analysis, as illustrated in Fig. 1.

There were no differences between the groups considering gender (female 60% vs. 69%, $p = 0.55$), mean age (53.5 vs. 47.5, $p = 0.15$), baseline HRDS (23.8 vs. 22.6, $p = 0.75$), number of failed medication trials (5.3 vs. 6.6, $p = 0.16$) or current psychotic traits (38% vs. 31%, $p = 0.66$), as illustrated in Table 1.

Comorbid psychiatric disorders (e.g. personality disorder or traits, substance abuse disorders, anxiety) were more common amongst the MDD group, as can be seen in supplementary table 1.

3.2. Response and remission rates

There was no significant difference in response (MDD 68% vs BPD 63%, χ^2, $p = 0.82$) or remission (MDD 35% vs BPD 54%, χ^2, $p = 0.23$), as seen in Table 1. This is in line with the meta-analysis of Dierckx et al. which showed comparable remission rates of around 50% in unipolar vs bipolar depression. (Dierckx et al., 2012) However, when examining psychotic features, we found a significantly higher response (non-psychotic 53% vs. psychotic 89%, χ^2, $p = 0.017$) and a trend towards a higher remission rate (non-psychotic 29% vs. psychotic 58%, χ^2, $p = 0.082$) in the psychotic group. This corresponds with the growing body of evidence that 'psychotic features' is one of the major determining factors for response or remission, and less so for older age or other demographics. Other previously identified predictive factors for ECT response are psychomotor retardation, higher severity of depression and

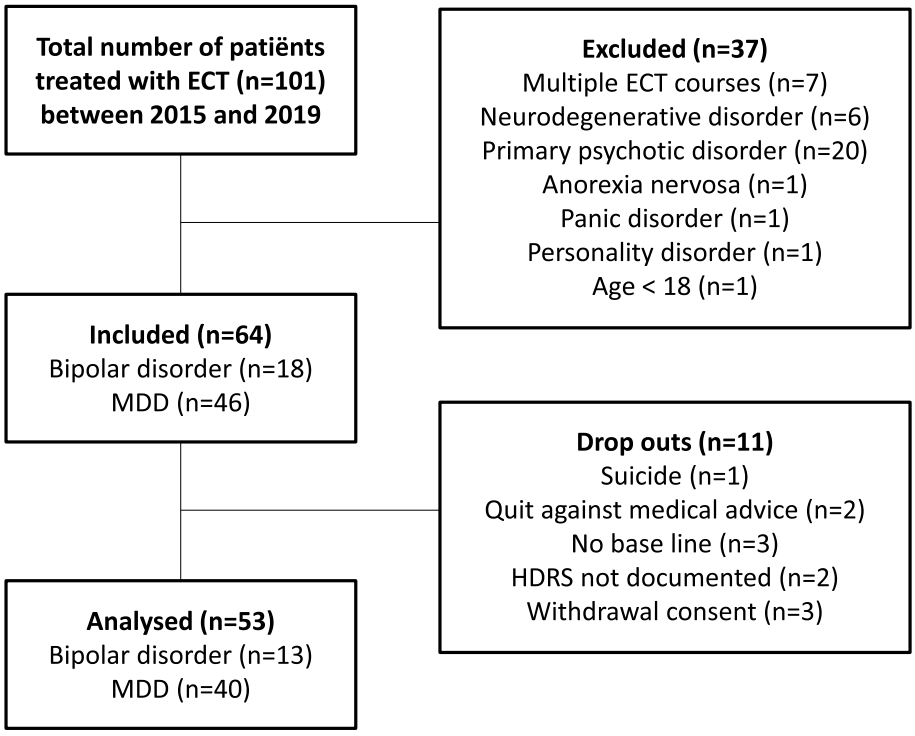

Fig. 1. Study flow diagram.

Table 1
Group characteristics and speed of response outcomes.

	Major depressive disorder (n = 40)	Bipolar depression (n = 13)	Test
Gender			$p = 0.55$ (χ^2)
Male	16 (40)	4 (31)	
Female	24 (60)	9 (69)	
Age (years)	53.5	47.5	$t = 1.33$, $p = 0.19$
Baseline HDRS (mean)	23.8	22.6	$U = 244$, $p = 0.75$
Failed medication trials	5.3	6.6	$U = 327.5$, $p = 0.26$
Psychotic features	15 (38)	4 (31)	$p = 0.66$ (χ^2)
Response	27 (68)	8 (62)	$p = 0.82$ (χ^2)
Speed of response (mean ECT)	10.4	7.1	$U = 67$, $p = 0.11$
Remission	14 (35)	7 (54)	$p = 0.23$ (χ^2)
Speed of remission (mean ECT)	10.8	9.0	$U = 49$, $p = 1$

Values shown as n (%) or mean. Statistics performed are either Mann Whitney *U* test or Chi-square. Speed of response and remission based on subset of patients that showed response/remission.

possibly melancholic features. (Heijnen et al., 2019; Van Diermen et al., 2018) In the BPD group it is notable that seven of the eight responders (88%) also achieved remission, against only 14 out of 27 (52%) in the MDD group, indicating that ECT treatment is associated with less residual depressive symptoms in patients with bipolar depression relative to MDD patients. Evidence suggests that comorbid personality disorders/traits (PD) are associated with worse outcomes in the treatment of depression. (Newton-Howes et al., 2014) As PD were more common in our MDD group, this could be a confounder for (speed of) response. However, in the current sample we did not find a significant difference in response in non-PD vs. PD patients (63% vs. 72%, χ^2, $p = 0.71$).

3.3. Speed of response

Concerning our main outcome speed of response, the bipolar group responded faster with a mean difference of 3.3 fewer ECT treatments to meet response criteria (whole group (n = 53) MDD 10.4 vs. BPD 7.1, p = 0.054). This is in line with a recent review that included ten studies reporting head-to-head on number of treatments of MDD versus BPD. None of those studies reported a slower response in BPD and five reported a (significantly) faster response of a mean of 1.5–3.6 fewer treatments needed. In the current study the direction of mean difference in number of treatments between MDD vs. BPD was comparable the direction reported in the meta-analysis, albeit not significant, possibly due to the low numbers of patients. However, we performed a multilevel regression model to examine which factors c.q. disorder fits the model of fast response. When analyzing the response/remitter group (n = 35), Model 1 outperformed Model 2, indicating a faster response for the bipolar group (AIC 252.83 vs 258.55, $\chi^2 = 11.72$, $p = 0.008$). These results suggest that there is an interaction effect of the number of treatments and bipolar disorder. To investigate how the decrease in HRDS differs between the two groups, we plotted the predictions made by Model 2, as seen in Fig. 2. Although there was a higher response rate in the psychotic group, the effect in number of treatments sessions was not found in the psychotic group (p = 0.225, Fig. 2a.). We did not find a difference in response rate or speed of response (p = 0.544, Fig. 2c.) between the PD and non PD group. These insights may help to clinically predict further response and manage expectations of patients, family and treatment team.

To explore possible confounding factors that may moderate faster response – e.g. personality disorders and traits – factors were added to the model, however the significance remained for the bipolar group (in the case of personality disorders/traits: AIC 256.15 vs 251.15, $\chi^2 = 6.99$, p = 0.008). Factors associated with refractoriness, such as number of failed medication trials and number of prior depressive episodes showed no interaction effects in our mixed effects models (failed trials: t = −0.753, p = 0.459; previous episodes: t = −1.158, p = 0.260). As all patients were treated in the same manner and through a standardized

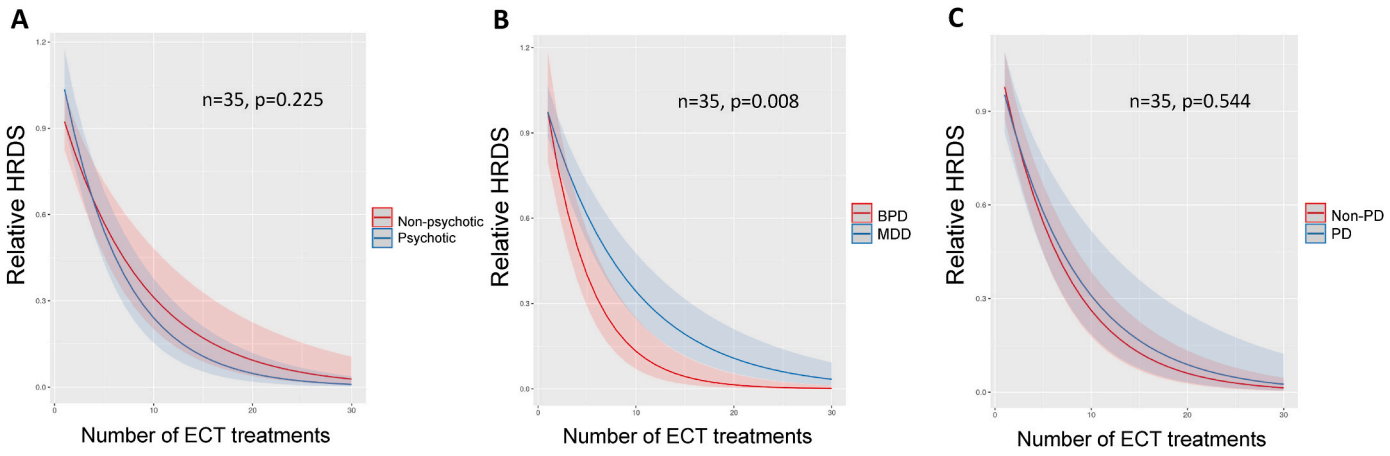

Fig. 2. Mixed effects regression models, Fig. 2. Mixed effects regression models for the response/remitter group (n = 35) for several possible predictive factors: (A) Psychotic versus non psychotic group, (B) MDD versus BPD group and (C) personality disorder (PD) and non-PD group.

protocol, regardless of diagnosis, technical aspects were unlikely to influence the speed of response. Electrode placement did not influence the speed of response: in 4 patients of the response/remitter group the placement was switched to bilateral, but only in the MDD group.

4. Discussion

In most international treatment algorithms for BPD (without psychotic features), ECT treatment is recommended after three failed medication trials or as a last step when most biological treatments failed. (Grunze et al., 2010; Malhi et al., 2015; Yatham et al., 2018). This study however, again shows that ECT in bipolar depression is effective and that response can be achieved fast, within several weeks. These insights, combined with the fact that ECT is safe and well tolerated, imply that ECT should not only be used as a 'last resort' in BPD.

Because of the fewer treatments needed to achieve response, patients with BPD may have fewer cognitive side-effects compared to patients with MDD. Some studies have shown a poorer cognitive performance with an increased number of treatments, therefore a faster speed of response may be beneficial. (Martin et al., 2015; Sackeim et al., 2008) This was however never shown in a prospective head-to-head study with a fast response group. (Kalisova et al., 2018; MacQueen et al., 2007; Sackeim et al., 2007) Thus further research is needed to evaluate whether a fast speed of response is associated with fewer cognitive side-effects.

The neurobiological basis underlying a faster speed of response in BPD is not known. As anticonvulsants mainly have a mood stabilizing effect in BPD, it is hypothesized that the powerful anticonvulsant properties of ECT induce a faster response in an anticonvulsant-sensitive disorder. Some studies noted that an increase in seizure threshold during the treatment trajectory predicts response, however only one study showed a higher percent increase in BPD compared to MDD. (Daly et al., 2001; Francis-Taylor et al., 2020; Gálvez et al., 2017)

4.1. Strengths and limitations

One of the strengths of this study is the naturalistic hospital clinical setting of the current cohort. Additionally, it is one of the few studies primarily aimed on speed of response in ECT. Another strength is that significant differences were found despite the low numbers, showing the robustness of the results. At the same time, this low number of participants is a limitation, as it may mask differences in patient characteristics and diminish interaction effects of other predictors of speed of response. Another strength is the way of participant selection, which is done automatically through the electronic patient system by searching patients receiving ECT, excluding a selection bias.

The most important limitations are the small sample and that the MDD group had more co-morbid psychiatric diagnoses with generally a high refractoriness, which may lead to a lower response in MDD. On the other hand, only a small portion of patients met criteria for a personality disorder and this factor did not influence the significance in the mixed effect regression model. Personality traits are more common in MDD and our sample thereby represents a real-life cohort. Furthermore, the exclusion of the drop out patients may have led to overestimation of the efficacy and speed of response (attrition).

5. Conclusion

To conclude, this chart review of a naturalistic academic hospital setting with comparable groups, shows an evident and clinically relevant faster speed of response for BPD relative to MDD. For further research, we suggest replicating these findings in larger prospective cohorts, mainly to validate clinical predictive factors for response and to investigate whether fewer treatments in BPD are also associated with fewer neurocognitive side effects.

Credit author statement

K.W.F. Scheepstra*: Conceptualization, Methodology, Investigation, Writing – original draft. J.B. van Doorn*: Methodology, Formal Analysis, Writing – original draft. D.S. Scheepens: Writing – Review & editing. A. de Haan: Investigation. N. Schukking: Investigation, Writing – Review & editing. J.B. Zantvoord: Writing – Review & editing. A. Lok: Conceptualization, Supervision, Writing – Review & editing. * shared first authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

KWF Scheepstra.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2022.01.008.

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