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Electroconvulsive therapy for depression with comorbid borderline personality disorder or post-traumatic stress disorder: A matched retrospective cohort study

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ABSTRACT

Background: The impact of comorbid borderline personality disorder (BPD) or post-traumatic stress disorder (PTSD) on clinical and cognitive outcomes of electroconvulsive therapy (ECT) in patients with major depressive episodes (MDE) is unknown.
Objective: Compare clinical response and adverse cognitive effects for MDE patients with comorbid BPD or PTSD to MDE only.
Methods: In a matched retrospective cohort study of 75 patients treated with ECT at an academic psychiatric hospital with DSM-IV MDE and either comorbid BPD, PTSD or both (MDE + BPD/PTSD), 75 MDE patients without BPD or PTSD (MDE-only) were matched. We reviewed clinical records to determine treatment response by estimating clinical global impression of improvement (c-CGI) and presence of adverse cognitive effects based on subjective distress or objective impairment. We explored factors associated with response and cognitive effects in the MDE + BPD/PTSD group.
Results: There was no difference in c-CGI response rates between groups ($p > 0.017$). Secondary analysis of inpatients found lower response rates for MDE + BPD (55.4%) and MDE + BPD + PTSD (55.8%) than MDE-only (82.5%), but not MDE + PTSD (65.0%). There was no difference in adverse cognitive effects in the MDE + BPD/PTSD (23.3%–26.8%) group compared to MDE-only (25.0%). In the MDE + BPD/PTSD group, factors associated with higher response rate were: referral indications other than failed pharmacotherapy, greater number of ECT treatments, presence of adverse cognitive effects, and seizure duration >30 s.
Conclusions: Despite a lower c-CGI response for inpatients with MDE + BPD, ECT is a viable treatment option for patients in the MDE + BPD/PTSD group with similar adverse cognitive effect profiles to MDE-only.

Introduction

Depression has recently become the leading cause of illness burden worldwide [1]. It is frequently treatment resistant, often when comorbid illnesses are present [2]. Two common comorbidities in patients with major depressive episodes (MDE) are borderline personality disorder (BPD) and post-traumatic stress disorder (PTSD): approximately 15–20% of patients with MDE meet criteria for either disorder [3,4]. Both BPD and PTSD have been associated with treatment resistance and worse clinical outcomes of MDE [5,6]. These two comorbidities also frequently co-occur, with up to 30% in epidemiologic samples [3] and greater than 50% in clinical samples [7] of patients with either BPD or PTSD meeting criteria for both diagnoses.

MDE that does not respond to several trials of pharmacotherapy or psychotherapy is considered treatment resistant and guidelines

Abbreviations: BL, bitemporal; BPD, borderline personality disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECT, electroconvulsive therapy; MDE, major depressive episode; PTSD, posttraumatic stress disorder; RUL, right unilateral; RUL-UB, right unilateral ultrabrief.

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recommend electroconvulsive therapy (ECT) [8]. Despite BPD and PTSD contributing to MDE treatment resistance, little is known about the impact of comorbid BPD or PTSD on ECT outcomes in patients with MDE. The only prospective controlled trial evidence comes from a single small (N = 20) trial in which patients with MDE and comorbid BPD experienced significantly lower remission rates than those with MDE alone [9]. Retrospective studies also suggest that BPD is associated with poorer short- and long-term clinical outcomes with ECT [10,11]. We are not aware of any similar prospective studies for patients with comorbid MDE and PTSD. In one retrospective study of patients with MDE and comorbid PTSD, the remission rate with ECT was 42% [12], which is lower than typical remission rates of 55–64% for MDE alone [13]. These studies did not examine factors associated with ECT outcomes in patients with MDE and comorbid BPD or PTSD. They also did not assess cognitive effects, which is an important knowledge gap because ECT-related cognitive effects are a major barrier to its broader implementation and use [14,15].

We sought to address these gaps using a representative sample of patients with MDE and comorbid BPD or PTSD, which would enable us to determine the relative impact of BPD and PTSD comorbidity on outcomes. Using a matched retrospective cohort design, our primary objective was to compare rates of ECT treatment response and adverse cognitive effects in patients with MDE with and without comorbid BPD or PTSD. Our secondary objective was to assess factors associated with these two outcomes in patients with MDE and comorbid BPD or PTSD.

Materials and methods

Study design and subjects

This study was conducted at the Centre for Addiction and Mental Health (CAMH), a 550-bed academic psychiatric hospital in Toronto, Canada that serves a population of three-million persons. It was approved by the CAMH research ethics board.

We completed a chart review including all 1645 referrals to the CAMH ECT program from October 2009 to October 2016. We abstracted the following from ECT referral forms completed by the referring psychiatrist: DSM-IV diagnosis, current psychotropic medications, clinical global impression of illness severity [16], and ECT indication. This information was verified by a review of the patient's medical record.

Patients were included if they met the following criteria: (1) a major depressive episode with a diagnosis of either unipolar depression or bipolar disorder; (2) a diagnosis of BPD, PTSD, or both; (3) they received at least one ECT treatment as part of an acute treatment course. Patients receiving maintenance or continuation ECT were not included.

Each patient with MDE and comorbid BPD or PTSD (MDE + BPD/PTSD group) was matched with one patient with MDE without BPD or PTSD (MDE-only group) based on: gender (male or female); diagnosis (unipolar vs bipolar depression); electrode placement (right-unilateral or bitemporal); and age (after other variables matched, the patient closest in age was selected to minimize individual age differences). Initially, we planned to also match based on admission status (i.e., inpatient vs. outpatient). However, the MDE + BPD/PTSD group was largely treated as inpatients and we were unable to find sufficient numbers of inpatients for the MDE-only group. Therefore, we also completed secondary analyses restricted to inpatients.

ECT treatment

Electrode placement was determined by the ECT psychiatrist based on variables such as risk of adverse cognitive effects, need for rapid response, and previous treatment protocols. The anesthetic agent used was methohexital 0.75–1.0 mg/kg IV and the muscle relaxant was succinylcholine 0.5–0.75 mg/kg IV. Labetalol IV was used as needed for hypertension, and granisetron or ondansetron IV were used for severe nausea. The ECT machine used was a MECTA spECTrum 5000Q with a fixed 800 milliamps parameter setting. A 1.0 ms (ms) pulse width was used for all bitemporal (BL) treatment sessions. For right unilateral (RUL) electrode placement the pulse width was set to an ultrabrief pulse width of 0.3–0.37 ms in more recent treatment courses, while the remainder received RUL with a pulse width of 1.0 ms. The stimulus titration method was used to determine seizure threshold of all patients. For determination of threshold, an adequate seizure was defined as a seizure lasting at least 15 s based on motor manifestation to ensure the seizure had generalized. After the threshold was determined, stimulus intensity was set at 1.5 times the seizure threshold for BL and 6 times the seizure threshold for RUL treatments.

Assessment of treatment response

Chart review

All patients who received at least one ECT treatment were eligible for assessment of treatment response. One author (TSK) reviewed all charts and estimated ECT response using methods from previous work [17,18]. Outcomes were assessed on a 4-point scale estimating clinician global impression improvement scale (CGI-I) [16] and yielded a clinical note CGI-I (c-CGI) score:

1 – Very much improved

Patient chart documented dramatic benefit from ECT treatment. Examples of this level of response: rapid discharge after treatment, reduction in need for medications, clear and complete resolution of target symptoms, and documentation such as “dramatic response” or “greatly improved”.

2 – Much improved

Patient chart documented benefit from ECT treatment. Examples: improvement justifying referral for maintenance ECT, substantial reduction in severity of target symptoms, and documentation such as “responded well”, or “good response”.

3 – Minimally improved

Patient chart documented some benefit from ECT treatment. Examples: slight or moderate reduction in severity of target symptoms, and documentation such as “improved somewhat”, or “partial response”.

4 – No improvement or worse

Patient chart documented minimal to no benefit from ECT treatment. Examples: treatment stopped after 1–2 sessions due to side effects, and documentation such as “no symptom changes”, or “no improvement noted”.

Based on c-CGI scores, patients were classified as treatment responders (c-CGI scores of 1 or 2) or non-responders (c-CGI score of 3 or 4).

Reliability

While attending (referring) psychiatrists were encouraged to complete the CGI-I after an ECT treatment course, this information was only available for a subset of patients in the study (N = 102). We used this subset of patients to assess agreement between c-CGI

(based on chart review) and CGI-I scores (provided by attending psychiatrists (see Appendix 1)). Overall, there was good agreement when classifying patients as responders versus non-responders (linearly weighted kappa = 0.70) [19]. A second author (DSG), blinded to the first author's ratings, reviewed a randomly selected subset of charts (n = 75) to assess the inter-rater reliability of the chart review method. Overall, there was good agreement when classifying patients as responders versus non-responders (linearly weighted kappa = 0.69) between chart reviewers.

Assessment of adverse cognitive effects

Chart review

As with treatment response, one author (TSK) reviewed all charts and assessed adverse cognitive effects as "clinically significant" or "not clinically significant." Clinically significant adverse cognitive effects were deemed to be present if any of the following were documented in the clinical record regarding cognitive effects:

1. Described as "significant", "major" or "severe"
2. Caused significant patient distress
3. Led to early discontinuation or altering ECT treatment course (e.g. a decrease in frequency of ECT treatments);
4. Associated with functional impairment (e.g., becoming lost while outside the hospital).

Reliability

In addition to a CGI-I, attending psychiatrists completed a similar clinician-rated scale assessing the level of adverse cognitive effects following completion of the acute ECT treatment course. These effects were rated as 'none', 'mild', 'moderate', or 'severe' in 102 of 150 patients. Considering adverse cognitive effects rated by physicians as 'none' or 'mild' to be "not clinically significant" and those rated as 'moderate' or 'severe' to be "clinically significant", there was a moderate agreement (linearly weighted kappa = 0.51) between clinical and chart review ratings of adverse cognitive effects (see Appendix 2). As with treatment response, a second author (DSG), blinded to the first author's ratings, reviewed a subset of randomly selected charts (n = 75) to assess the inter-rater reliability of the chart review method for assessment of adverse cognitive effects. Overall, there was moderate agreement (linearly weighted kappa = 0.60) between chart reviewers.

Data analysis

For our primary objective, we compared rates of treatment response and adverse cognitive effects between patients with MDE-only and MDE with comorbid BPD, PTSD or both in combination. Due to potentially therapeutic effects of an inpatient admission [20] and differing rates of admission status (i.e. inpatient vs outpatient) for MDE-only vs. MDE + BPD/PTSD we also completed a secondary analysis restricted to inpatients.

For our secondary objective, in the MDE + BPD/PTSD group we compared characteristics, clinical indications, and ECT treatment characteristics between treatment responders and non-responders. We also used multivariate logistic regression models to determine the independent contributions of characteristics that were potentially associated with ECT treatment response, and presented the results for each variable as odds ratios (OR) and 95% confidence intervals (CI). We entered the following covariates into the initial model: age, BPD diagnosis, PTSD diagnosis, admission status (using outpatient treatment as reference), intermittent or regular benzodiazepine use, antipsychotic use, antidepressant use, and anti-epileptic use. We then used a backward stepwise selection and removed variables according to model contribution to create the final model. We then completed an analysis comparing characteristics, clinical indications, and ECT treatment characteristics in patients with and without adverse cognitive effects. For patients who received multiple ECT treatment courses, the index course was used for analysis and subsequent courses were included for descriptive purposes.

We compared continuous data with a Student's t-test to compare means, and categorical data with chi-squared analysis or a Fisher's exact test for 2 × 2 comparisons. All tests were two-tailed and significance was set at an alpha level of 0.05, except for comparisons between diagnoses of treatment response and adverse cognitive effects for which the significance level was set at 0.017, using a Bonferroni correction for three comparisons (MDE-only vs MDE + BPD, MDE + PTSD, and MDE + BPD + PTSD). All analyses were performed using SPSS 23.0 (IBM Corporation, Armonk New York, USA).

Results

Demographic and clinical characteristics (see Table 1)

We identified 75 patients in the MDE + BPD/PTSD group who received a total of 99 courses of acute ECT during the study period. There were 57 patients with BPD, 62 patients with PTSD, and 44 patients with both BPD and PTSD. For patients with BPD, 77.2% had comorbid PTSD and for patients with PTSD 71.0% had comorbid BPD. Seventy-five matched patients in the MDE-only group received a total of 95 courses of acute ECT. There was no difference in the date of index ECT referral relative to study entry between the MDE-only vs MDE + BPD/PTSD group (p = 0.78). Compared to MDE-only, patients in the MDE + BPD/PTSD group were older, had a more severe depression, were more likely to have a history of trauma, and to be treated concurrently with antipsychotics, antidepressants, and benzodiazepines in an inpatient setting.

ECT characteristics (see Table 2)

Patients in the MDE + BPD/PTSD group had a significantly shorter seizure duration compared to patients with MDE-only. Groups did not differ significantly in electrode placement changes or number of repeat ECT courses. There were four patients, all in the MDE + BPD/PTSD group, treated with standard width RUL electrode placement.

ECT treatment response

Rates of treatment response did not differ between MDE-only (64.0%) patients with MDE + BPD (54.4%), MDE + PTSD (62.9%), or MDE + BPD + PTSD (54.5%; p for three comparisons > 0.017) (see Fig. 1). There was no difference in the distribution of c-CGI scores between diagnostic categories compared to MDE-only (MDE + BPD: $\chi^2 = 2.96$, p = 0.40; MDE + PTSD: $\chi^2 = 1.09$, p = 0.78; MDE + BPD + PTSD: $\chi^2 = 2.50$, p = 0.47). There was no difference in mean c-CGI between MDE-only (2.3 ± 1.0) and MDE + BPD (2.4 ± 1.0), MDE + PTSD (2.3 ± 0.9), or MDE + BPD + PTSD (2.5 ± 1.0; p for three comparisons > 0.017).

Restricting analysis to inpatients only, there was a significant difference between response rates in patients with MDE + BPD and MDE-only (55.4% vs. 82.5%; Fisher's p = 0.008) and those with MDE + BPD + PTSD and MDE-only (55.8% vs. 82.5%; Fisher's p = 0.010). Response rates in patients with MDE + PTSD and MDE-only did not differ significantly (65.0% vs 82.5%; Fisher's p = 0.070). Given the inpatient analysis was a secondary analysis, with 3 additional comparisons, using a Bonferroni corrected p-value of 0.0083 (0.05/6) results in a significant difference in response rates between inpatients with MDE-only and MDE + BPD (p < 0.0083).

Table 1
Clinical and demographic characteristics of included patients (N = 150).

	MDE and BPD or PTSD (N = 75)	MDE only (N = 75)	Fisher's Exact P-value**
Clinical Characteristics			
Age (years) – Mean ± SD; [Min-Max]	38.1 ± 12.7 [18–71]	43.9 ± 13.1 [18–82]	<**0.05****
MDE CGI Severity – Mean ± SD	5.5 ± 0.6	5.1 ± 0.8	<**0.05****
Female Gender	73 (97.3%)	73 (97.3%)	**'—**
Unipolar MDE	64 (85.3%)	64 (85.3%)	**'—**
Bipolar MDE	11 (14.67%)	11 (14.67%)	**'—**
Psychotic Features	8 (10.7%)	5 (6.7%)	0.56
BPD	57 (76.0%)	0 (0%)	**'—**
PTSD	62 (83.0%)	0 (0%)	**'—**
Combination BPD and PTSD	44 (58.7%)	0 (0%)	**'—**
History of Self-Harm	49 (65.3%)	2 (2.7%)	**0.0001**
Traumatic Experiences*			
No/Unknown Trauma	10 (13.3%)	66 (88.0%)	**0.0001**
Interpersonal Violence (Physical, Emotional, Sexual, Occupational)	64 (85.3%)	9 (12.0%)	**0.0001**
Witnessed Trauma or Accident	9 (12.0%)	0 (0%)	**0.003**
Multiple Traumas	22 (29.3%)	2 (2.7%)	**0.0001**
History of Childhood Trauma	52 (69.3%)	8 (10.7%)	**0.0001**
Medications during ECT			
Antipsychotic	62 (82.7%)	45 (60.0%)	**0.004**
Antidepressant	73 (97.3%)	64 (85.3%)	**0.02**
Mood stabilizer/AED	10 (13.3%)	4 (5.3%)	0.16
Lithium	2 (2.7%)	3 (4.0%)	1
Benzodiazepine (intermittent or regular)	59 (78.7%)	27 (36.0%)	**0.0001**
Treatment Setting			
Inpatient	72 (96%)	40 (53.3%)	**0.0001**
Involuntary Inpatient	5 (6.7%)	4 (5.3%)	1

All values are presented as n (%) unless indicated otherwise.
*Patients may have had multiple traumas hence number of traumas of each type will sum to greater than 100%.
**Bolded value indicates statistical significance $p < 0.05$.
***Student's t-test p-value, df = 148.
Abbreviations: Anti-epileptic drug (AED), borderline personality disorder (BPD), clinical global impression (CGI), electroconvulsive therapy (ECT), major depressive episode (MDE), posttraumatic stress disorder (PTSD), standard deviation (SD).

Table 2
ECT characteristics.

	MDE and BPD or PTSD (n = 75)	MDE only (n = 75)	Fisher's exact P-Value**
ECT Indication*			
Failed pharmacotherapy	65 (86.7%)	66 (88.0%)	1
Prior good response to ECT	10 (13.3%)	15 (20.0%)	0.381
Suicidality	24 (32.0%)	13 (17.3%)	0.057
Failed continuation maintenance pharmacotherapy	5 (6.7%)	7 (9.3%)	0.765
Intolerance of adequate pharmacotherapy	6 (8.0%)	6 (8.0%)	1
Patient preference	16 (21.3%)	8 (10.7%)	0.118
ECT Electrode Placement			
RUL	43 (57.3%)	42 (56.0%)	1
RUL to BL	17 (22.7%)	18 (24.0%)	1
BL	13 (17.3%)	15 (20.0%)	0.834
BL to RUL	2 (2.7%)	0 (0%)	0.497
RUL-UB****	56 (93.3%)	60 (100%)	0.119
Number of Treatment Courses			
One course	52 (69.3%)	55 (73.3%)	1
Two courses	15 (20.0%)	15 (20.0%)	1
Three courses	4 (5.3%)	4 (5.3%)	1
Four + courses	4 (5.3%)	1 (1.3%)	0.366
Other			
Number of acute treatments – Mean ± SD [Min-Max]	10.6 ± 4.6 [1–20]	10.8 ± 4.7 [2–20]	>0.05***
<8 ECT Treatments	18 (24.0%)	17 (22.7%)	1
EEG Seizure Length (s) – Mean ± SD [Min-Max]	46.8 ± 15.9 [18.4–77.3]	52.7 ± 19.9 [26.8–146.1]	<**0.05*****
Previous Course of ECT	18 (24.0%)	19 (25.3%)	1

All values are presented as n (%) unless indicated otherwise.
* Some patients have multiple indications.
**Bolded p-value indicates statistical significance $p < 0.05$.
***Student's t-test p-value, df = 148.
****% is based on all RUL electrode placements (N = 60).
Abbreviations: Bitemporal (BL), borderline personality disorder (BPD), electroencephalography (EEG), electroconvulsive therapy (ECT), major depressive episode (MDE), posttraumatic stress disorder (PTSD), right unilateral (RUL), standard deviation (SD).

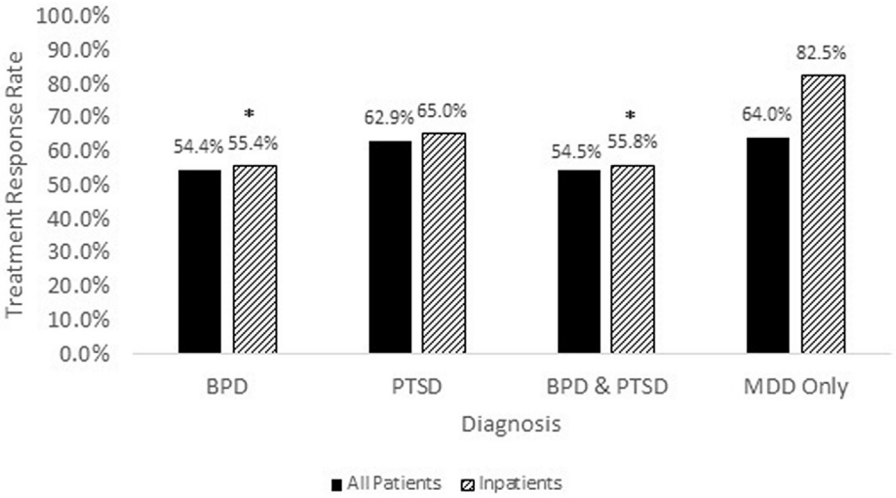

Fig. 1. Treatment response among patients with MDE and comorbid BPD (N = 57), PTSD (N = 62), or BPD and PTSD (n = 44), and MDE only (N = 75). For all patients, there was no significant difference in treatment response between diagnoses (p > 0.017). Restricting analysis to inpatients only resulted in significantly lower response rates for comorbid BPD (Fisher's exact p = 0.008) or BPD & PTSD (Fisher's exact p = 0.010), but not PTSD without BPD (p = 0.070) compared to MDE only. *Indicates statistically significant p controlling for three comparisons: p < 0.017.

There was no difference in the distribution of c-CGI scores between diagnostic categories compared to MDE-only (MDE + BPD: χ^2 = 8.18, p = 0.042; MDE + PTSD: χ^2 = 3.72, p = 0.29; MDE + BPD + PTSD: χ^2 = 7.05, p = 0.070). There was a difference in mean c-CGI between MDE-only (2.0 ± 0.8) with MDE + BPD (2.5 ± 1.0; p = 0.017), or MDE + BPD + PTSD (2.5 ± 1.0; p = 0.015) but not MDE + PTSD (2.3 ± 0.9; p = 0.10).

We also restricted analyses to patients who had an adequate course of ECT (defined as ≥8 treatments). Rates of treatment response in patients with MDE-only (68.9%) did not differ from MDE + BPD (70.7%; Fisher's p = 1.0), MDE + PTSD (72.9%; Fisher's p = 0.68), or MDE + BPD + PTSD (68.8%; Fisher's p = 1.0). There was no difference in the distribution of c-CGI scores between diagnostic categories compared to MDE-only (MDE + BPD: χ2 = 0.26, p = 0.97; MDE + PTSD: χ2 = 1.73, p = 0.63; MDE + BPD + PTSD: χ2 = 1.48, p = 0.69). There was no difference in mean c-CGI between MDE-only (2.2 + 0.9) and MDE + BPD (2.2 + 0.8), MDE + PTSD (2.2 + 0.8), or MDE + BPD + PTSD (2.3 + 0.8; p for three comparisons > 0.017) patients. Given the finding for inpatients with MDE + BPD or MDE + BPD + PTSD having lower response rates, we repeated the inpatient analysis for these two groups with patients who received an adequate ECT course and found no difference in response rates with MDE-only (85.3%) and MDE + BPD (70.0%; Fisher's p = 0.17) as well as MDE + BPD + PTSD (68.8%; Fisher's p = 0.15).

For patients in the MDE + BPD/PTSD group, treatment response was associated with referral for failed pharmacotherapy, larger number of ECT treatments, absence of adverse cognitive effects, and seizure duration >30 s (see Table 3). For patients treated with standard pulse width RUL, 2/4 patients had a treatment response.

In the regression model, covariates associated with treatment response were lack of BPD diagnosis (OR = 3.8; 95%CI = [1.6–9.0]), inpatient treatment (OR = 5.9; 95%CI = [2.3–15.2]), and number of ECT treatments (OR = 1.1; 95%CI = [1.0–1.2]).

Adverse cognitive effects associated with ECT

Rates of adverse cognitive effects did not differ between the four diagnoses (MDE + BPD: 26.3%, MDE + PTSD: 22.6%, MDE + BPD + PTSD: 25.0%, MDE-only: 30.7%; p for three comparisons > 0.017) or when restricting analysis to inpatients (MDE + BPD: 26.8%, MDE + PTSD: 23.3%, MDE + BPD + PTSD: 25.6%, MDE-only: 25.0%; p for three comparisons > 0.017) (see Fig. 2).

In the MDE + BPD/PTSD group, adverse cognitive effects were associated with fewer ECT treatments (see Table 4). For patients treated with standard pulse width RUL, 1/4 patients had adverse cognitive effects.

Discussion

Using a matched retrospective cohort study, we examined treatment response and adverse cognitive effects of ECT in patients with MDE and comorbid BPD or PTSD compared to patients with MDE only. Among those who received ECT as inpatients (72/75 MDE + BPD/PTSD group and 40/75 MDE-only group), c-CGI response rates were significantly lower for patients with MDE and comorbid BPD. This finding was confirmed in a regression analysis in which BPD was independently associated with lower rate of treatment response. It is also consistent with prior research which found that patients with MDE and BPD have worse ECT treatment outcomes compared to MDE alone [9]. A major contributor to this finding was the differing response rates for the MDE-only group as a whole (64.0%) compared to the inpatient subset (82.5%). This suggests ECT is either uniquely efficacious for inpatients with MDE-only, or more likely, there were unobserved confounding factors that lead to lower observed response rates in outpatients. We suspect our analysis restricted to inpatients is more accurate as patients are more likely to be closely matched on observed and unobserved confounding factors such as symptom severity and therapeutic environment [20,21]. MDE patients with comorbid PTSD but not BPD had lower response rates than those with MDE only (65.0% vs 82.5%) but the difference did not reach statistical significance. This is suggestive of decreased response rates to ECT, as PTSD comorbidity has been associated with worse depression outcomes for combined pharmacotherapy/psychotherapy [22,23], psychotherapy alone [24], and hospital admissions [6]. As the current study is the first comparing ECT treatment outcomes in depressed patients with and without PTSD, future studies will be required to clarify this potential finding. We also found, in an urban psychiatric hospital ECT clinic, that BPD and PTSD were comorbid with each other in >70% of patients, which suggests if one comorbidity is present then there is a high probability of the other.

Table 3
Factors associated with treatment response in patients with MDE and comorbid BPD or PTSD (N=75).

	Clinical Response (n = 46)	Minimal/No Clinical Response (n = 29)	Fisher's exact P-Value*
Demographic and Clinical Characteristics			
Age (years) – Mean ± SD	38.3 ± 13.2	37.7 ± 12.1	>0.05**
MDE CGI Severity – Mean ± SD	5.5 ± 0.7	5.4 ± 0.6	>0.05**
Unipolar MDE	41 (89.1%)	23 (79.3%)	0.319
Bipolar MDE	5 (10.9%)	6 (20.7%)	0.319
Psychotic Features	7 (15.2%)	1 (3.4%)	0.141
History of Childhood Trauma	32 (69.5%)	20 (69.0%)	1
History of Self-Harm	30 (65.2%)	19 (65.5%)	1
Medications during ECT			
Antipsychotic	38 (82.6%)	24 (82.8%)	1
Antidepressant	45 (97.8%)	28 (96.5%)	1
Mood Stabilizer/AED	5 (10.9%)	3 (10.3%)	1
Lithium	0 (0%)	2 (6.9%)	0.146
Benzodiazepine (any use)	34 (73.9%)	25 (86.2%)	0.256
Benzodiazepine (regular use)	11 (23.9%)	12 (41.4%)	0.129
Referral Indication			
Failed pharmacotherapy	44 (95.6%)	21 (72.4%)	**0.011**
Prior good response to ECT	5 (10.9%)	5 (17.2%)	0.496
Suicidality	12 (26.1%)	12 (41.4%)	0.207
Failed continuation maintenance pharmacotherapy	3 (6.5%)	2 (6.9%)	1
Intolerance of adequate pharmacotherapy	3 (6.5%)	3 (10.3%)	0.671
Patient preference	9 (19.6%)	7 (24.1%)	0.773
ECT Characteristics			
Number of treatments – Mean ± SD	12.2 ± 3.5	8.1 ± 5.1	<**0.05****
<8 Treatments	4 (8.7%)	14 (48.3%)	<**0.001**
Started with RUL Treatment	37 (80.4%)	22 (75.9%)	0.773
Electrode Placement Change	12 (26.1%)	7 (24.1%)	1
Adverse Cognitive Effects	7 (15.2%)	11 (37.9%)	**0.030**
EEG Seizure Length > 30s	43 (93.5%)	9 (31.0%)	<**0.001**

All values are presented as n (%) unless indicated otherwise.
*Bolded p-value indicates statistical significance $p < 0.05$.
**Student's t-test p-value, df = 73.
Abbreviations: Anti-epileptic drug (AED), bitemporal (BL), borderline personality disorder (BPD), clinical global impression (CGI), electroencephalography (EEG), electroconvulsive therapy (ECT), major depressive episode (MDE), posttraumatic stress disorder (PTSD), right unilateral (RUL), standard deviation (SD).

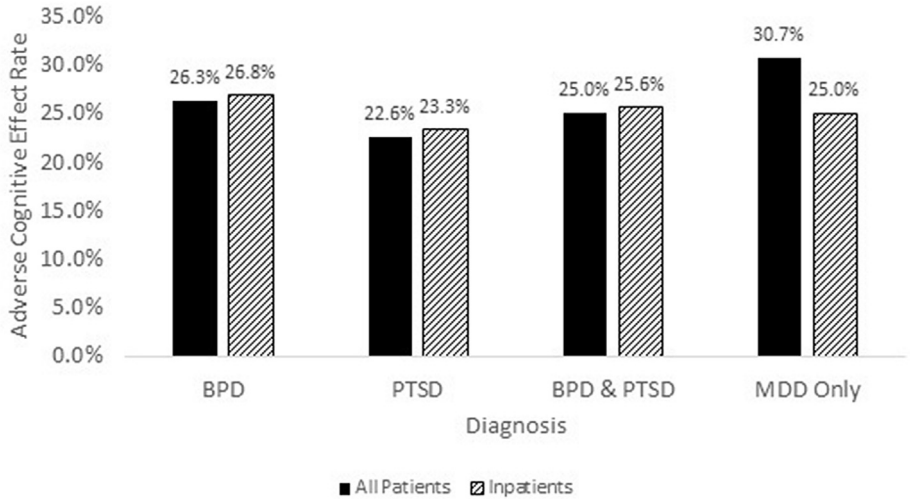

Fig. 2. Adverse cognitive effects associated with ECT among patients with MDE and comorbid BPD (N = 57), PTSD (N = 62), or BPD and PTSD (N = 44), and MDE only (N = 75). For all patients and inpatients only, there was no significant difference in treatment response between diagnoses (p for three comparisons > 0.017).

We did not find that comorbid BPD or PTSD was associated with any significant differences in the rate of adverse cognitive effects. Thus, despite reduced response rates for inpatients, ECT may be a viable treatment option in patients with depression and comorbid BPD, PTSD, or combined BPD and PTSD particularly when an adequate course (≥8 treatments) of ECT is delivered.

We also identified several factors associated with treatment response in the MDE + BPD/PTSD group. A higher rate of response to ECT was associated with referral for failed pharmacotherapy, a larger number of ECT treatments, absence of adverse cognitive effects, and a longer seizure length. Similarly, our regression model identified BPD diagnosis, inpatient treatment and number of ECT treatments as characteristics associated with treatment response. Seizure length is a factor that can be modified by discontinuing benzodiazepines, which have been shown to reduce seizure duration [25,26] and worsen ECT outcomes [27]. In our study, patients in the MDE and comorbid BPD or PTSD group were more than twice as likely to receive benzodiazepines than those with MDE only. Though we did not find a difference in treatment response between patients receiving vs not receiving benzodiazepines, guidelines

Table 4
Factors associated with adverse cognitive effects for patients with MDE with comorbid BPD or PTSD (N=75).

	No Cognitive Effects (n = 57)	Cognitive Effects (n = 18)	Fisher's exact P-Value*
Demographic/Clinical			
Mean age (years)	38.3 ± 13.6	37.4 ± 9.8	0.793
BPD Diagnosis	42 (73.7%)	15 (83.3%)	0.534
PTSD Diagnosis	48 (84.2%)	14 (77.7%)	0.499
Medications			
Mood Stabilizer/AED	6 (10.5%)	2 (11.1%)	1
Lithium	2 (3.5%)	0 (0%)	1
Benzodiazepine Use - Regular or Intermittent	45 (78.9%)	14 (77.8%)	1
Benzodiazepine Use - Regular	18 (31.6%)	5 (27.8%)	1
ECT Characteristics			
Mean number of treatments	11.3 ± 4.6	8.6 ± 4.2	**<0.05****
<8 Treatments	11 (15.8%)	7 (33.3%)	0.116
BL Treatment (Started with)	11 (19.3%)	4 (22.2%)	0.747

All values are presented as n (%) unless indicated otherwise.
*Bolded p-value indicates statistical significance $p < 0.05$.
**Student's t-test p-value, df = 73.
Abbreviations: Anti-epileptic drug (AED), bitemporal (BL), borderline personality disorder (BPD), electroconvulsive therapy (ECT), major depressive episode (MDE), post-traumatic stress disorder (PTSD).

encourage clinicians to minimize or eliminate benzodiazepine use prior to ECT [8]. The association between treatment response and number of ECT treatments suggests that the reduced response rate in patients with MDE + BPD may be partially attributable to the number of ECT treatments received, because inpatients with MDE + BPD who received an adequate course had similar response rates to MDE-only patients. However, the results of our regression model suggest an independent contribution of both BPD diagnosis and number of ECT treatments.

Adverse cognitive effects were also an important factor in MDE + BPD/PTSD group treatment response: treatment responders experienced a lower rate of adverse cognitive effects (15.2%) than non-responders (37.9%). Furthermore, adverse cognitive effects were paradoxically associated with a lower number of ECT treatments (mean of 8.6 vs. 11.3 in those without adverse cognitive effects). These findings can potentially be explained by adverse cognitive effects occurring early during ECT treatment course leading to premature discontinuation of ECT and subsequent treatment non-response. This model is supported by a previous study in which subjective memory complaints occurred as early as after one ECT treatment [28].

In the current study, we also compared several demographic and clinical characteristics between patients with and without comorbid BPD or PTSD. Patients with comorbid BPD or PTSD had significantly higher severity of illness, higher rates of antipsychotic, antidepressant, and benzodiazepine treatment, and were more likely to be treated as inpatients. These findings confirm that patients with comorbid BPD or PTSD referred for ECT present as more severely ill than those without comorbidity.

Strengths and limitations

To our knowledge, this is the largest study to examine treatment outcomes of ECT in patients with MDE and comorbid BPD and the first study in patients with MDE and comorbid PTSD. It is also the only study to, albeit crudely, assess cognitive outcomes of ECT in patients with MDE and BPD or PTSD. While several of our results are clinically relevant, some limitations need to be considered. First, given the retrospective study design, we can identify associations but cannot establish causality and the inability to blind outcome assessment is a possible source of bias in the findings. Despite using matching and statistical analyses to account for group differences, the results are potentially impacted by the lack of randomization and associated unobserved and residual confounding. There were also baseline differences between MDE-only and MDE + BPD/PTSD groups potentially impacting treatment response. The MDE + BPD/PTSD group was both older and had more severe symptoms. However, these characteristics are associated with improved response to ECT [21,29], and therefore our results may underestimate the difference in treatment response between MDE-only and patients with MDE and comorbid diagnoses. The advantage of the retrospective cohort design is that it can include a clinically representative group of patients (i.e., all those with comorbid BPD or PTSD), and our results are consistent with existing prospective and retrospective studies [9–11]. Second, one of the patient characteristics we were unable to account for was additional comorbid disorders, such as substance use or anxiety disorders, which given their prevalence in patients with BPD or PTSD [3], may also influence our results. This will be an important area of further study. Third, our outcome assessments were global, rather than domain-specific. The c-CGI and measure of adverse cognitive effects based on a chart review prevent us from characterizing which symptoms improved (e.g., distinguishing extent to which global clinical improvement was due to improved mood versus improved BPD or PTSD symptoms). However, improvement measured by c-CGI had a good agreement with improvement reported by treating psychiatrists, consistent with our previous study [17]. Our assessment of adverse cognitive effects included both subjective (patient distress) and objective (early ECT discontinuation and functional impairment) assessments; however, this measure is unable to determine which cognitive domains were impacted by ECT. Last, our finding of reduced response rates for MDE + BPD compared to MDE-only patients was based on secondary analyses and while we attempted to be conservative in our use of statistical significance, it must be interpreted in this context.

This work also highlights several areas for future study. Prospective trials should use validated symptom scales such as the Hamilton Depression Rating Scale [30], Clinician Administered PTSD Scale [31], or Zanarini Rating Scale for Borderline Personality Disorder [32] to determine which symptom domains improve with treatment. Future studies should also include objective measures of cognition using tools such as the ECT Cognitive Assessment tool that also assesses specific cognitive domains that may be affected by ECT [33].

Conclusion

We did not find a difference in response rates between diagnostic groups; however, the secondary analysis of inpatients found those with MDE and comorbid BPD were significantly less likely to respond to ECT compared to matched patients without comorbid

BPD or PTSD. Encouragingly, there were no differences in rates of cognitive adverse effects between those with or without comorbid BPD or PTSD. Several factors were associated with a better treatment response in patients with MDE and BPD or PTSD, including referral for ECT because of failure to respond to pharmacotherapy, larger number of ECT treatments, absence of adverse cognitive effects, and seizure duration >30 s. Overall, this study suggests that ECT is a viable treatment option for a subset of patients with MDE and comorbid PTSD or BPD and there is no increased rate of cognitive adverse effects; however, clinicians should be mindful of an attenuated response rate in admitted patients with these comorbidities. Future prospective trials incorporating standardized symptom rating scales and cognitive measures are needed.

Declaration of interest

TSK has received research support from the University of Toronto and the Clinician Scientist Program through the Department of Psychiatry at the University of Toronto. ZJD in the last 3 years has received research and equipment in-kind support for an investigator-initiated study through Brainsway Inc and Magventure Inc. ZJD has also received monies for participation on an advisory board from Sunovion Inc. Finally, ZJD owns>$10,000 (CAD) in stock of Biogen Inc. BHM currently receives research financial support from Brain Canada, the CAMH Foundation, the Canadian Institutes of Health Research (CIHR), the US Patient-Centered Outcomes Research Institute (PCORI), and the US National Institute of Health (NIH); and in kind support from Capital Solution Design LLC (software used in a study founded by CAMH Foundation), Eli Lilly (medications for a NIH-funded clinical trial), Capital Solution Design LLC (software used in a study founded by CAMH Foundation), HAPPYneuron (software used in a study founded by Brain Canada), and Pfizer (medications for a NIH-funded clinical trial). Within the past five years he has also received research support from Bristol-Myers Squibb (medications for a NIH-funded clinical trial). He directly owns stock of General Electric (less than $5000). DMB receives research support from the Canadian Institutes of Health Research (CIHR), Brain Canada, Weston Brain Institute, National Institutes of Health (NIH), Temerty Family through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Family Research Institute. He received non-salary operating funds and in-kind equipment support from Brainsway Ltd. for an investigator-initiated study. He is the site-principal investigator for three sponsor-initiated clinical trials from Brainsway Ltd. He received in-kind equipment support from Tonika/Magventure for an investigator-initiated study. He received medication supplies from Indivior for an investigator-initiated trial.

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Appendix 1. Responder vs non-responder agreement (kappa = 0.70) between clinical note CGI and clinician CGI (n = 102)

		Clinician CGI	
		Response	Non-Response
Clinical Note CGI	Response	**65**	2
	Non-response	11	**24**

Bolded values indicate agreement between clinician CGI and clinical note CGI.

Appendix 2. Presence vs absence of clinically significant adverse cognitive effects (kappa = 0.51) between chart review and clinician rated (n = 102)

		Clinician Rated	
		Present	Absent
Chart Review	Present	**64**	6
	Absent	14	**18**

Bolded values indicate agreement between clinician assessment of significant cognitive impairment and chart review assessment of significant cognitive impairment.

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