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A Retrospective Analysis of the Impact of Electroconvulsive Therapy on Anxiety Severity in Patients with Treatment Resistant Depression

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Abstract

A Retrospective Analysis of the Impact of Electroconvulsive Therapy on Anxiety Severity in Patients with Treatment Resistant Depression

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Background

In major depressive disorder (MDD), anxiety is present in 40-60% of patients. Electroconvulsive therapy (ECT) is an effective treatment for treatment-resistant depression (TRD). There is limited data regarding the improvement of symptoms of anxiety in patients receiving ECT for TRD.

Methods

A retrospective chart review of TRD patients who received an acute ECT course in an outpatient setting was conducted. Symptomatic response was measured using the Beck Depression Inventory-II (BDI-II) and Generalized Anxiety Disorder-7 Scale (GAD7). Two generalized estimating equation (GEE) models were conducted to assess the degree of change in anxious symptoms relative to the change in depressive symptoms. The GEE models also included pre-treatment depression scores and ECT electrode placement (right unilateral, bifrontal, bitemporal) as covariates.

Results

117 patients with unipolar or bipolar depression were analyzed. Symptoms of both depression (-0.09, $p < 0.001$) and anxiety (-0.08, $p < 0.001$) improved after ECT treatment, with a greater standardized decrease for symptoms of depression. Higher levels of anxiety were associated with a smaller improvement in depression.

Conclusions

Co-occurring symptoms of anxiety in TRD patients are not a contraindication for ECT. However, anxiety symptoms show a more modest improvement throughout an acute course and their presence may be associated with a smaller improvement in depression. This knowledge may play a role in decisions regarding treatment options for TRD patients.

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Background

Major Depressive Disorder (MDD) is one of the most common psychiatric disorders in both specialist and general medical practice (Voineskos et al., 2020). Despite the high prevalence of MDD, significant disparities remain in treatment. Of the 14 million people who suffer from depression, approximately 30% of patients do not respond to any conventional treatment (Al-Harbi 2012).

Treatment resistant depression (TRD), typically defined as a failure to respond to at least two separate antidepressant trials of adequate dose and duration in the current depressive episode, affects approximately a third of patients diagnosed with MDD with a lifetime prevalence of 1-5% of patients (Nemeroff 2007). TRD contributes disproportionately to the cost and functional burden of MDD. Direct and indirect health care resource utilization costs are nearly double for TRD patients versus non-TRD MDD patients and quadruple in comparison to non-MDD patients (Amos et al., 2018). Individuals with TRD demonstrate functional impairment equal to or above that associated with other severe chronic medical conditions such as diabetes and congestive heart failure (Hays et al., 1995).

Depression and anxiety are the most prevalent coexisting psychiatric conditions, with 40-60% of MDD patients experiencing anxiety symptoms (Baldwin et al., 2002; Gaspersz et al., 2017a). The co-occurrence of anxiety symptoms or disorders has significant implication for MDD disease course and burden. First, when anxiety is co-morbid with MDD, the progression of the disease is more refractory to standard antidepressant treatment (Goldberg et al., 2012; Ge et al., 2021). Secondly, coexisting anxiety symptoms make treating MDD more difficult than MDD

without anxiety symptoms (Gaspersz et al., 2017b). Thirdly, individuals with depression and co-morbid anxiety disorders or symptoms are at greater risk of suicide (Pfeiffer et al., 2009). Fourthly, anxiety symptoms in patients with MDD are associated with increased use of health care resources (McLaughlin et al., 2006). Residual anxiety symptoms following improvements in depressive symptoms place patients at greater risk for relapse or recurrence of another depressive episode (Scholten et al., 2023; see Hershenberg et al., 2022).

Antidepressants and psychotherapy are two primary treatments for depression (Cuijpers et al., 2014). Electroconvulsive therapy (ECT) is reserved as a neuromodulation treatment in TRD patients for whom pharmacotherapy and psychotherapy have been ineffective and symptom presentation is severe (Li et al., 2020). Indeed, ECT is an efficacious treatment, even in patients who do not respond to antidepressants or psychotherapy (Husain et al., 2004; Spaans et al., 2015). Although electroconvulsive therapy (ECT) is widely recognized for its effectiveness, it is not typically chosen as an early treatment option due to the potential cognitive side effects and the risks associated with the procedure. (Getty and Faziola, 2017).

Despite the well-documented antidepressant effects of ECT for TRD patients, very little is known about the potential anxiolytic effects of ECT for TRD patients. Although there is a strong co-occurrence between depression and anxiety symptoms, the wealth of ECT studies primarily examines the extent to which ECT improves depression symptoms and neglects an examination of the extent to which ECT can treat co-occurring symptoms of anxiety (APA, 2001; Wait and Easton, 2013). Initial evidence suggests that anxiety may lower the response rate to ECT, but that its presence should not be an exclusionary factor for receiving ECT (Steinholtz et

al., 2021). In one study of patients receiving a course of bitemporal ECT, anxiety symptoms improved less than depression symptoms (Huang et al., 2019). In another study, ECT patients with primary anxiety disorders and mixed psychopathology including depression demonstrated clinical improvement (Yahya and Khawaja, 2021). In a study of 70 bipolar patients in a depressed or mixed episode who received a bilateral course of ECT twice weekly, ECT was shown to be an effective depression treatment, but patients with anxiety disorders relapsed in a shorter time (Medda et al., 2020; see Hershenberg et al., 2022 for a review).

The goal of the present study is to examine the extent to which anxiety symptom severity improves, relative to improvements in depressive symptoms, in TRD patients receiving an acute course of ECT. We analyzed retrospective study data in a naturalistic cohort of outpatients seeking a course of ECT for unipolar or bipolar depression. Consistent with the small but growing body of research, we hypothesized that anxiety symptoms would decrease in an acute ECT course, but that this change would be less robust than changes in symptoms of depression.

Methods

Participants

Retrospective data from participants aged 18 years and older from the Treatment Resistant Depression Clinic at [institution blinded for review] who were referred for and received a course of ECT were included in the present study. The TRD clinic serves a consultative role to referring community clinicians with regard to diagnosis and treatment planning, and offers interventional psychiatric treatment options for their patients with TRD,

including ECT. 88.1% of patients evaluated in the clinic have failed three or more antidepressant trials in the current episode. Analyses included 117 participants who, having been evaluated in the TRD clinic, consented to using their clinical data for research purposes, received a primary mood disorder diagnosis, initiated an acute course of ECT between Oct 2018 to July 2023, and completed patient reported outcome scales assessing their depression and anxiety throughout the course of treatment.

The protocol was approved by the Institutional Review Board (IRB00093806); the IRB approved data inclusion and analysis for all clinic patients, including those previously collected under a quality assurance project. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Procedures and Measures

Participants completed patient reported outcome scales, including the Beck Depression Inventory (BDI-II; Goegan et al., 2022) and the Generalized Anxiety Disorder-7 (GAD7; Tsygankova et al., 2021), to assess their baseline depression and anxiety severity prior to their first ECT treatment. Patient reported outcome scales were assessed throughout the treatment course prior to treatments 4, 6, 8, 12, and every session after the twelfth.

ECT psychiatrists determine the number and frequency of ECT sessions for each patient that characterize their acute course based on overall clinical improvement, typically ranging from

8-12 sessions.

ECT Procedures

Generalized tonic-clonic seizure (GTC) was induced with electrical stimuli delivered by either a MECTA Spectrum 5000 or Thymatron ECT device per the manufacturer's protocol. All patients received a general anesthetic followed by 0.75-1.5 mg/kg succinylcholine as the muscle relaxant. The seizure threshold (ST) was determined at first treatment using the titration method with an algorithm of stimulations (Enns and Karvelas, 1995). Most patients started ultra-brief right unilateral (UBRUL) protocol and were adjusted to bifrontal (BF) or bitemporal (BT) as clinically necessary. Following the institutional RUL treatment protocol, each patient received an electrical stimulus dose 6x the initial ST after the first treatment sessions with an increase to 8x ST if no response occurred after the fifth or sixth treatment. Escalation to 10x ST was pursued before if no demonstrable clinical improvement with stimulation at 8x ST. After 10x ST, lead placement switch from UBRUL to brief pulse bifrontal (BF) or bitemporal (BT) was considered. Psychotropic medications were continued in all patients; however, an attempt was made to reduce benzodiazepines to the minimal tolerated dose to minimize impact on seizure threshold. Flumazenil was given prior to treatment in patients who remained on benzodiazepines during treatment. Anticonvulsants and mood stabilizers were held the night before ECT treatment to ensure adequate seizures. Additionally, lithium was held the night before treatment to mitigate post-ictal agitation or delirium. Patients included in analyses initiated ECT treatment in an outpatient setting. A modality switch was captured in the data as a change from UBRUL to BF, BT, or any combination thereof, and included as a covariate in all analyses.

Mood and Anxiety Assessments

During the acute course of treatment, patients completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) questionnaire to assess changes in depressive symptoms. The BDI-II is a 21-item measure of depression severity with responses ranging from 0 to 3 and a total score ranging from 0 to 63, with scores greater than 29 suggestive of *severe* depression. Baseline BDI-II values from our sample demonstrated good reliability (Cronbach's alpha = 0.86). Patients also completed the Generalized Anxiety Disorder-7 Scale (GAD7; Spitzer et al., 2006; Kneipp et al., 2010) to assess anxiety symptoms, with responses ranging from 0 to 3 and a total score ranging from 0 to 21, with scores 10 and above suggestive of *moderate* anxiety and 15 and greater suggestive of *severe* anxiety. Baseline GAD7 values from our sample demonstrated good reliability (Cronbach's alpha = 0.86).

Statistical Analysis

To assess the degree of change in anxiety symptoms during an acute course of treatment, and to understand this change relative to change in depressive symptoms, two generalized estimating equation (GEE) models were calculated. GEE is an extension of generalized linear models (GLMs), ideal for analyzing longitudinal, inter-correlated data. GEE achieves an extra level of robustness by inferring the correlations between observations and creates a system for performing inference using a mean model approach. Two GEE models were used to analyze changes in depression and anxiety severity over time in an acute ECT course. The first GEE model analyzed changes in depression levels across treatment. BDI-II score was the dependent variable, and Baseline BDI-II, modality switch, time, and GAD7 were the independent variables.

The second GEE model analyzed changes in anxiety throughout ECT treatment with GAD7 as the dependent variable. Baseline BDI-II, modality switch, and time were the independent variables. Two-tailed $p < 0.05$ was considered statistically significant. Before the models were executed, longitudinal BDI-II, GAD7 and baseline BDI-II scores were standardized to z scores for cross-model comparisons on magnitude changes in the dependent variables. Finally, non-standardized variables were used to calculate clinical response, defined as a 50% or greater reduction from first to final treatment in the acute series, to qualitatively describe the percentage of the sample demonstrating clinically meaningful changes in symptoms of depression and anxiety, respectively. Corresponding remission rates calculated by values at the final treatment session were not compared due to the restricted range of the GAD7 (0-21) compared to the BDI-II (0-63).

Results

This analysis included data from 117 patients (64.10% women, mean age 53.59 (*sd* = 16.10)). Patients had a diagnosis of unipolar or bipolar depression. As shown in Table 1, most patients had baseline depression scores that placed them in the *severe* range and baseline anxiety symptoms in the *moderate* range. 61% of patients had a past psychiatric hospitalization and nearly one-third of patients reported a past suicide attempt (See Table 1).

As shown in Table 2 and Figure 1, for the first GEE model predicting changes in depression, BDI-II severity was shown to significantly decrease over the course of ECT (-0.09, $p < 0.0001$). An increase in each treatment session was associated with a 0.09 standard deviation decrease in BDI-II z scores while controlling for baseline BDI-II, GAD7, and modality switch.

Baseline BDI-II had a positive effect on BDI-II (0.37, $p < 0.0001$), indicating that the higher the initial depression z scores, the higher the subsequent scores in depression throughout treatment. Additionally, the level of GAD7 played a role in the severity of BDI-II over the course. Specifically, GAD7 over the treatment had a significant and positive effect on BDI-II ($p < 0.001$), indicating that the higher the anxiety scores, the higher the scores in depression throughout the course of the treatment. Last, modality switch had a positive effect on BDI-II z scores (0.39, $p < 0.0001$); changing modality was associated with a 0.39 increase in standard deviation of BDI-II z scores throughout the treatment.

As shown in Table 3 and Figure 1, for the second GEE model predicting changes in anxiety, GAD7 significantly decreased throughout the ECT series (-0.08, $p < 0.0001$). An increase in time was associated with a 0.08 standard deviation decrease in GAD7 z scores while controlling for baseline BDI-II and modality switch. Baseline BDI-II z scores had a significant and positive effect on GAD7 z scores (0.40, $p < 0.0001$), indicating that the higher the initial depression scores were, the higher the subsequent scores in GAD7. Patients presenting with higher anxiety were not more likely to undergo modality switches, as modality switch was not significantly associated with GAD7 scores (see Table 2 and Figure 1).

Non-standardized variables were used to calculate clinical response rates, and depression and anxiety total scores at the final treatment are displayed in Figures 2 and 3. Almost half (49.57%) of patients showed a clinical response on the BDI-II, and 43.59% of patients showed a clinical response on the GAD7.

In sum, findings illustrate that anxiety symptoms did significantly improve throughout the course of an acute course of ECT, change that was similar to, but not quite as robust, as improvements in depression. Importantly, higher levels of anxiety were associated with a smaller improvement in depression. Taken together, these findings may suggest that anxiety can indeed improve throughout an ECT course but that its presence may reduce the overall antidepressant effectiveness of ECT.

Discussion

A review of the current literature reveals limited data surrounding the impact of ECT on anxiety severity in TRD patients. While ECT is well-established for its antidepressant effects, its impact on co-occurring anxiety has been largely understudied in patients with unipolar and bipolar depression. The present study sought to investigate the impact of an acute course of ECT on anxiety severity in a highly symptomatic and highly generalizable outpatient TRD sample, hypothesizing that anxiety symptoms would decrease in an acute ECT course, but that this change would be less robust than changes in symptoms of depression.

In support of our hypothesis, a statically significant reduction occurred in both depression and anxiety severity after the acute ECT series. Moreover, when analyzing data with standardized GEE models, anxiety severity showed a smaller magnitude of decrease over the course of ECT in comparison to depression severity. For every unit increase in time, there was a corresponding decrease of 0.09 standard deviation in depression, compared to a decrease of 0.08 standard deviation in anxiety. Rates of clinical response followed a similar pattern. Consistent

with the larger literature, this could suggest that an acute ECT series has a more consistent and pronounced effect on reducing depression severity compared to anxiety severity in TRD patients. In this manner, results are consistent with prior work demonstrating that an acute ECT course can be an effective treatment in alleviating co-morbid anxiety symptoms, but anxiety symptoms may improve less than core features of depression (Huang et al., 2019; Marino and Friedman, 2013; Yahya and Khawaja, 2021).

Importantly, the presence of prominent symptoms of both depression and anxiety together may be a marker for more severe and refractory patients (Hershenberg et al., 2022), consistent with our finding that higher anxiety was a significant predictor of depressive symptoms by the close of the acute course. Depression and anxiety, while often co-occurring, likely have shared and divergent pathophysiological mechanisms. This would account for the benefit of anxiety from ECT, a robust antidepressant, but also a different and more complicated trajectory of improvement when both co-occur. Finally, the significant association between modality switch and increased depression severity aligns with the clinical practice of implementing a modality switch when a patient is not showing adequate antidepressant improvement. This supports current guidelines for implementing individualized treatment approaches in TRD, in which treatment modality is adjusted to optimize outcomes.

Several limitations exist in this study. Firstly, inherent complications in retrospective chart review include, but are not limited to, variance in the quality of treatment information recorded at treatment and lack of randomization procedures. Secondly, there was limited data regarding the patients' use of psychiatric medications such as benzodiazepines, which may decrease the clinical efficacy of ECT (Delamarre et al., 2019). Further, the study did not include

seizure threshold as a covariate. Finally, the study used a naturalistic cohort of unipolar and bipolar patients. Anxiety symptoms may appear differently in patients with unipolar versus bipolar depression, and due to the size of the sample, we were not able to control for other medical and psychiatric co-morbidities, age, gender, and treatment response status. While the size and scope of the real-world nature of the sample limits statistical inference, it also provides a highly generalizable sample of ECT patients as it is routinely practiced in the community, which provides unique insight into the effectiveness of ECT in a clinical setting, complementing more tightly controlled experimental designs (Kerner and Prudic, 2014).

Taken together, this study suggests that ECT is a safe and effective treatment for TRD, including when patients present with co-occurring symptoms of anxiety. On the one hand, anxiety symptoms show a favorable trajectory of improvement, though to a lesser extent than depressive symptoms. Nevertheless, while anxiety is not a contraindication for ECT, its presence at the start of the acute course may portend a less favorable antidepressant course. The interconnected relationship between depression and anxiety continues to highlight the need for comprehensive approaches in TRD treatment and continues to demonstrate the complexity of treating patients for whom anxiety and depression co-occur, as core depressed mood improvements, absent from improvements in anxiety, may be an ongoing risk factor for relapse and recurrence.

Table 1. *Descriptive Statistics*

Variable	Mean (SD) / n (%)
Age (years)	53.59 (16.10)
Biological sex	
Female	75 (64.10%)
Male	42 (35.90%)
Race/ethnicity	
Asian/Pacific Islander	3 (2.56)
Black	8 (6.84)
White	104 (88.89)
Multi-race	2 (1.71)
Years of education (bachelor's degree or higher)	82 (70.10)
Employment status (disability/unemployed)	33 (28.21)
History of >/1 psychiatric hospitalization	71 (60.68)
History of >/1 suicide attempt	33 (28.21)
Baseline BDI-II	32.17 (10.631)
Baseline GAD7	13.48 (5.160)

Table 2. *Parameter estimate for a GEE Model Fitted to Estimate Variation in standardized BDI-II over the course of ECT treatment*

Independent Variable	Coefficient Estimate	SE	z	P value	95% Confidence Interval	
Intercept	0.43	0.053	65.80	<.001***	0.32	0.53
Time	-0.09	0.0072	152.56	<.001***	0.10	-0.075
Baseline BDI-II	0.37	0.048	57.67	<.001***	0.27	0.46
GAD7	0.42	0.047	80.92	<.001***	0.33	0.51
Modality Switch	0.39	0.095	17.23	<.001***	0.21	0.58

Table 3. *Parameter estimate for a GEE Model Fitted to Estimate Variation in standardized GAD7 over the course of ECT treatment*

Independent Variable	Coefficient Estimate	SE	z	P value	95% Confidence Interval	
Intercept	0.60	0.078	59.40	<.001***	0.45	0.75
Time	-0.08	0.009	78.79	<.001***	-0.098	-0.062
Baseline BDI-II	0.40	0.071	32.74	<.001***	0.27	0.54
Modality Switch	-0.020	0.15	0.02	0.89	-0.31	0.27

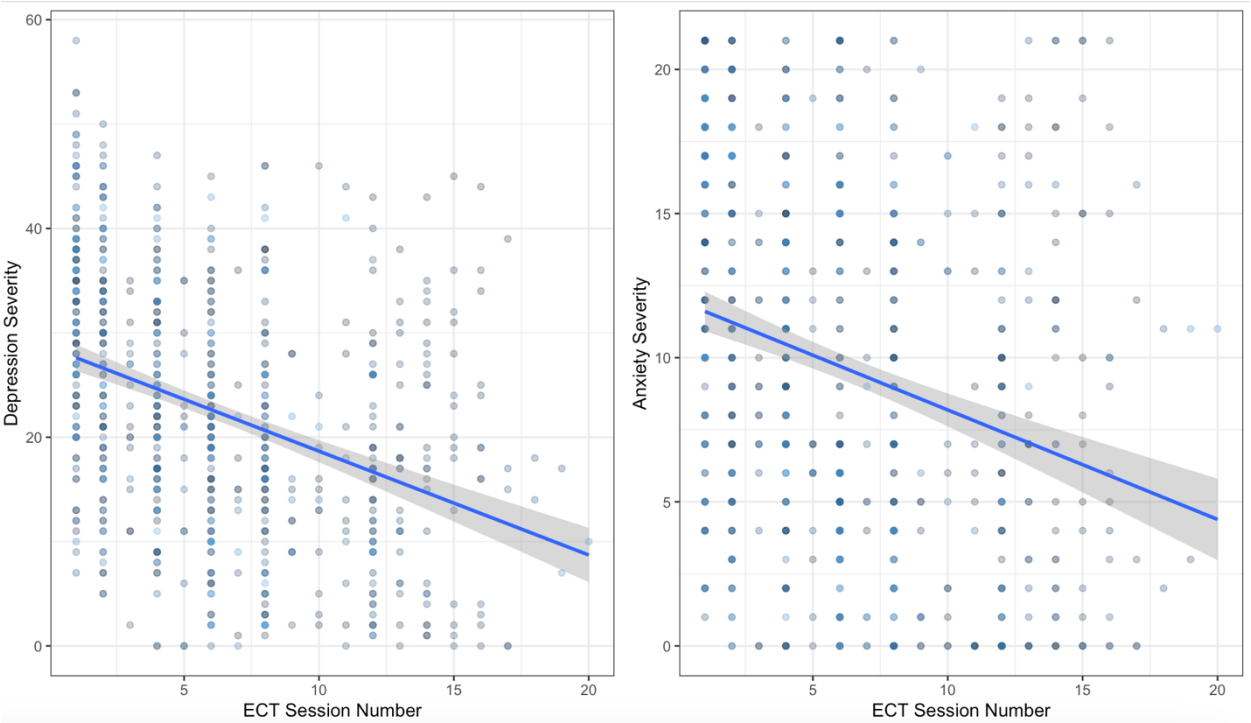

Figure 1: *From left to right: Two scatterplots representing depression severity (BDI-II) and anxiety severity (GAD7) throughout ECT series.* *The OLS regression lines (blue) and confidence envelope (grey, shaded area) are also displayed to demonstrate trend of depression and anxiety levels over time.*

Figure 1. *Linear regression to illustrate the trajectory of depression and anxiety severity, respectively, over the course of up to 20 ECT sessions.*

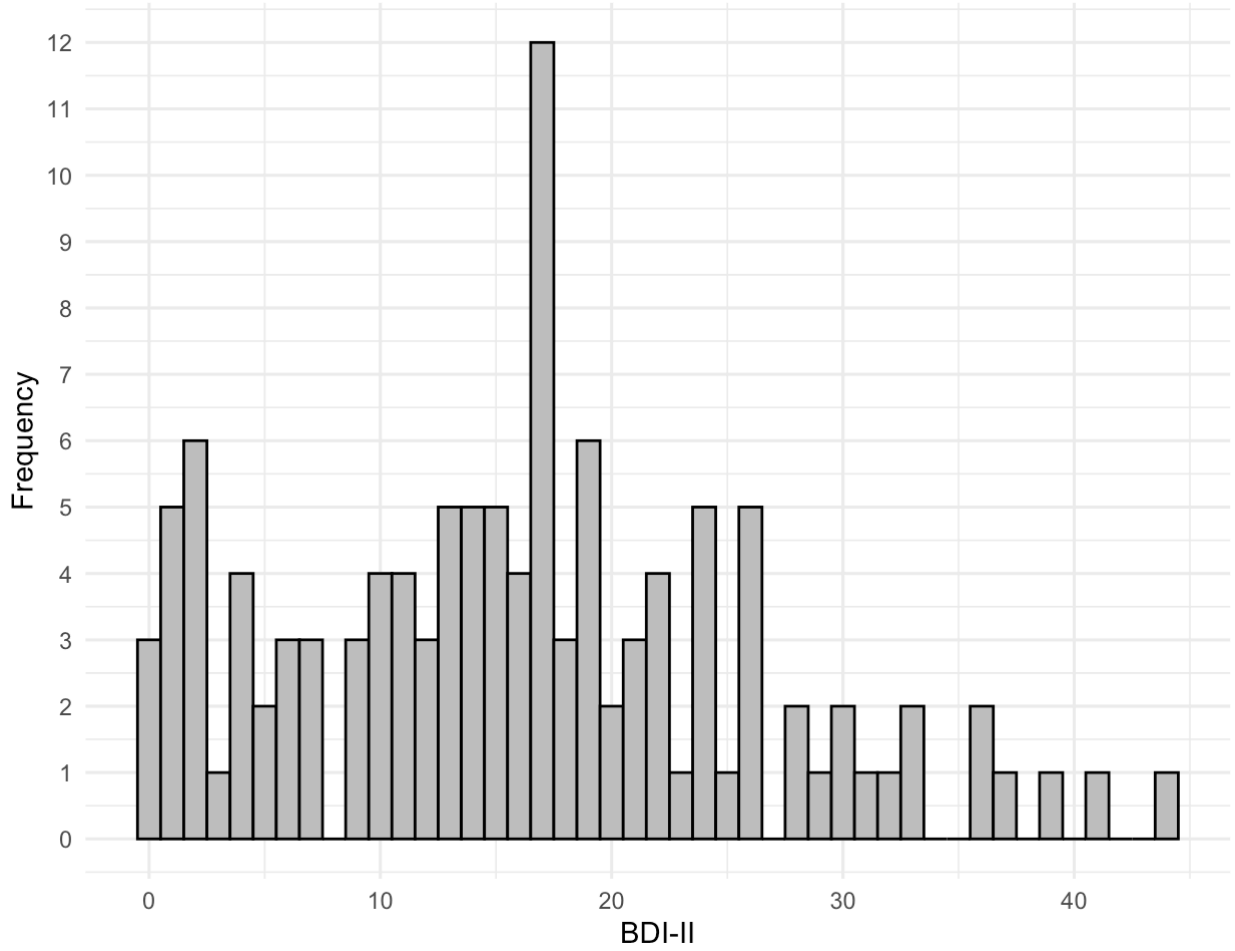

Figure 2. *Histogram of final BDI-II scores at the last session of the acute course*

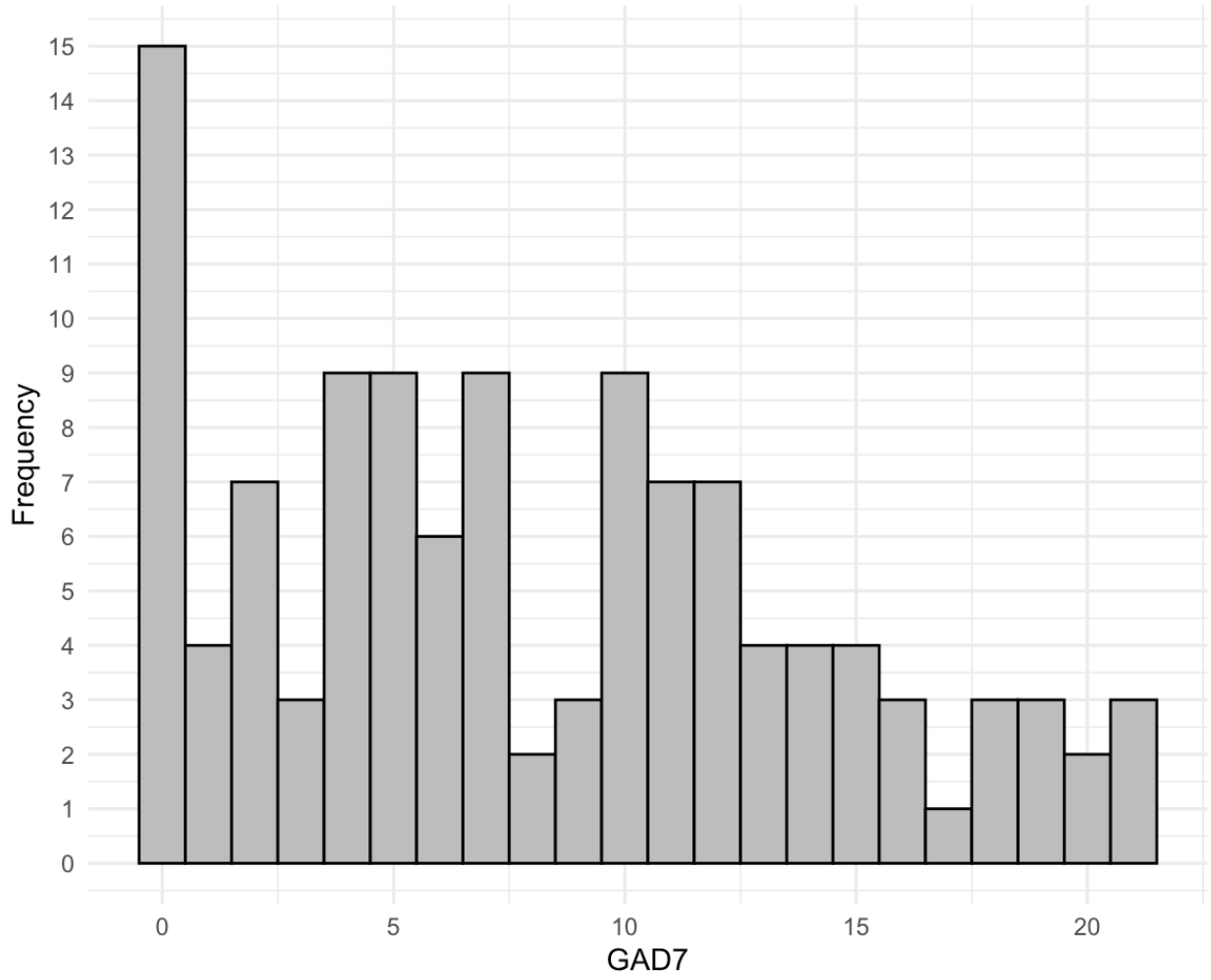

Figure 3. *Histogram of final GAD7 scores at the last session of the acute course*

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