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Relief of expressed suicidality in schizophrenia after electroconvulsive therapy: A naturalistic cohort study

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ABSTRACT

Suicide risk in schizophrenia is a significant treatment challenge but there are few approved treatments. Electroconvulsive therapy (ECT) is a highly effective treatment for suicidality in depression but its effect on suicidality in schizophrenia is unclear. We conducted a retrospective naturalistic study of the real-world effect of ECT on expressed suicidality as assessed by item 4 of the 24-item Brief Psychiatric Rating Scale in 113 patients with treatment resistant schizophrenia receiving ECT. 19.5% of patients expressed suicidal ideation pre-ECT of which 86.4% experienced an improvement in expressed suicidality after an average of 10.2 (SD 2.7) sessions of ECT. Changes in suicide scores before and after ECT was examined using a generalized estimating equation (GEE) model which showed that the effect of ECT on suicide was significantly mediated by depression and explained 72.2% of the decreased in expressed suicidality. ECT is effective in decreasing depression and expressed suicidality in patients with schizophrenia and should be considered as a treatment option for managing suicidality and psychosis in patients with treatment resistant schizophrenia.

1. Introduction

Schizophrenia is a chronic severe mental illness with premature mortality that is partially accounted for by increased suicides (Palmer et al., 2005). The lifetime risk of suicide in schizophrenia is estimated to be as high as 13% (Drake et al., 1985) and 8.5 fold that of the general population (Harris and Barraclough, 1997). Despite this high risk of suicide, there are few approved treatments to address suicidality in schizophrenia (Kasckow et al., 2011). Only clozapine is US FDA approved to treat suicidality in schizophrenia (Meltzer et al., 2003) and SSRIs may be helpful to decrease suicidality in schizophrenia (Zisook et al., 2010).

Electroconvulsive therapy (ECT) is the oldest somatic treatment modality in psychiatry still in current use (Cerletti and Bini, 1938). It is the most effective acute treatment for severe depression (Carney et al., 2003) and also effective in reducing psychotic symptoms in treatment resistant schizophrenia (American Psychiatric Association, 2008; Petrides et al., 2014; Tharyan and Adams, 2005). ECT is highly effective in rapidly decreasing suicidality in depression (Fink et al., 2014; Kellner et al., 2005; Prudic and Sackeim, 1999) and can be life saving for some patients. However, the effect of ECT on suicidality in schizophrenia is unclear. We thus set out to investigate the effect of ECT on expressed suicidality in schizophrenia in a large naturalistic cohort of patients with treatment resistant schizophrenia receiving ECT.

Singapore is a small nation state at the tip of the Malaysian archipelago. It has a population of approximately 5.5 million people consisting of 74.3% ethnic Chinese, 13.3% Malays and 9.1% Indian (Department of Statistics Singapore, 2016). The Singapore Institute of Mental Health (IMH) is the only tertiary psychiatric hospital in Singapore and has 1900 inpatient beds and about 40,000 outpatients. The IMH treats about 80% of the national load of patients with schizophrenia. At the IMH, ECT is prescribed primarily for schizophrenia (47%) with schizoaffective disorder (20.3%), depression (20.4%) and mania (6.8%) being the other major indications. ECT was effective in treating psychotic symptoms in 64.5% of patients with schizophrenia and also improved cognitive functioning in these patients (Tor et al., 2017). We conducted a retrospective study of the effects on expressed suicidality of ECT treatment given in a real-world setting to patients with schizophrenia, by analyzing an existing clinical database of patients with schizophrenia who were referred for ECT.

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2. Methods

2.1. ECT delivery

ECT was delivered by a specialized medical team consisting of 2 consultants and 2 medical officers trained in ECT technique to ensure consistent delivery of ECT. Individualized dosing based on each patient's empirically determined seizure threshold was used. ECT was delivered using a Thymatron system IV device (Somatics, USA) from Jan 2016 to Dec 2016 and a MECTA SpECTrum 5000Q device (MECTA, USA) from Jan 2017 onwards with hand held electrodes. ECT was given with either bitemporal, right unilateral (d'Elia position (d'Elia, 1976)) or bifrontal electrode positioning (Abrams and Taylor, 1973). Bitemporal ECT was delivered at 0.5 ms pulsewidth at 1.5x seizure threshold, bifrontal ECT was delivered at 1.0 ms pulsewidth at 1.5x seizure threshold and right unilateral ECT was delivered at 0.5 ms pulsewidth at 5x seizure threshold as per IMH clinical ECT treatment protocols. Propofol was used for anesthesia at 1 mg/kg and suxamethonium was used as the muscle relaxant at 0.5 mg/kg.

2.2. Participants

Patients were referred to the ECT service by psychiatrists who diagnosed schizophrenia by clinical assessments based on DSM-IV / DSM-V or ICD-10 criteria. Patients were referred due to poor response to standard medication treatment as assessed clinically by their psychiatrists. Patients who received and completed ECT at the IMH between Jan 2016 and Jan 2018 and who had at least a baseline pre-ECT BPRS rating were included in this retrospective study.

2.3. Outcome measures

During the study, ratings (symptom, cognitive and global assessment of function) were performed at baseline (1–2 days before ECT) and after the acute course of ECT (1–2 days after the last ECT treatment). The primary effectiveness outcome was response as assessed by the Brief Psychiatric Rating Scale (BRPS) (Overall and Gorham, 1962) for psychotic symptoms using the accepted response criterion of 40% improvement from baseline scores (Petrides et al., 2014). Psychotic, Mania and Depressive symptom subscales were derived from the BRPS scores (Burlingame et al., 2006). The primary cognitive outcome was change in the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). Specific Singaporean versions of MoCA in the local languages (English, Chinese, Malay, Tamil) were used. The Global assessment of function (GAF) was used to assess overall functioning in patients (Hall, 1995).

BPRS ratings were done by two ECT medical officers who underwent BPRS rater training using standardized training videos under the supervision of PCT. Intraclass correlations, as defined by (MSrater − MSerror)/[MSrater + (average number of patients per rater − 1)*MSerror] between the BPRS raters and PCT were 0.77 and 0.87 . Cognitive outcomes (MoCA) were administered by ECT nurses. These nurses were trained by PCT, who had received training in the administration of these scales from a registered neuropsychologist and researcher at the University of New South Wales (Sydney) (DM). In addition, the nursing staff were certified by DM for the administration of the MoCA.

Question 4 of the BPRS measured expressed suicidality on a 7-point Likert scale with "1″ being no suicidality and "7″ being highly suicidal. This item was used as the main outcome of interest in the analysis. We grouped patients into 2 groups based on their score on question 4 of the BRPS: Non- suicidal (score = 1) and Suicidal (score > 1).

Data was collected in the clinical ECT service using the CARE (Clinical Alliance and Research in ECT) framework (Martin et al., 2018). Ethical approval for accessing, analyzing and reporting data was obtained from the local institutional research ethics board (DSRB CRC 510–2015).

2.4. Statistics

Statistical analyses were conducted using STATA version 13.1 and MPLUS software version 7.4. Descriptive analyses were first conducted to describe sociodemographic and clinical characteristics of the sample (Age, gender, BRPS psychotic, manic, depressive subscales, MoCA and GAF). The depressive subscale did not include the item on expressed suicidality. Differences between the non-suicidal group and suicidal groups in demographic and clinical characteristics were examined using independent *t*-test for continuous variables and chi-squared tests for categorial variables. Patients were divided into groups based on their change in BPRS expressed suicidality, psychotic, manic and depressive subscales (improved or worsened after ECT) and odds ratio calculated for the association between change in expressed suicidality and change on the BPRS psychotic, mania and depressive subscales respectively. Changes in suicide scores (BPRS item on suicidality) before and after ECT was examined using a generalized estimating equation (GEE) model (which is preferable to conventional methods for repeated measures (Ma et al., 2012)) as an extension of generalized linear models for repeated measures data, accounting for confounding variables age, gender, number of ECT and BPRS sub scores and repeated observation effects in our dataset. To examine whether changes (post ECT minus pre ECT scores) in depression, mania and psychotic symptoms subscale scores may mediate the relationship between ECT and changes (post ECT minus pre ECT scores) in suicide score, mediation analyses were performed using MPLUS software version 8.2. The significance of indirect effects was tested using bias-corrected bootstrap confidence intervals estimated based on 10,000 bootstrapped samples as recommended by MacKinnon et al. (2004). It is statistically significant different if the lower and upper bounds of a 95% confidence interval do not contain zero. In the mediation model, direct effect refers to the effect of ECT on changes in suicide scores without the mediating effects, while indirect effects refer to the effect of ECT on changes in suicide scores via the mediators including changes in depression, mania and psychotic symptoms. Total effect refers to the combination of both direct and indirect effects of ECT on changes in suicide score. Statistical significance was set at $p < 0.05$, using two-sided tests.

3. Results

We had complete data for 113 patients with schizophrenia who received ECT and who had a baseline BRPS. 86.4% (19 of 22) of patients in the suicidal group experienced an improvement in their expressed suicidality score. The odds ratio for improvement in expressed suicidality was significant only for improvement in the depressive subscale (OR = 2.92, $\chi^2 = 3.887$, df = 1, $p = 0.049$). Differences between the non-suicidal and suicidal group are detailed in Table 1 and changes in raw suicidality scores are shown in Table 2.

A bivariate GEE model demonstrated that there was a significant reduction in suicide scores after ECT (1.142 ± 0.498 vs. 1.460 ± 1.078, Mean Difference = −0.319, p value = 0.002). After controlling for age, gender, number of ECT and changes in psychotic, mania and depression scores in GEE model, the reduction was not significant (p-value = 0.328). However, we found depression (beta = 0.130, p value < 0.001) was significantly and positively associated with suicide. It shows that the reduction in suicide scores was significantly associated with reduction in depression score.

To understand the effect of ECT on suicide which might be explained by the changes in psychotic, mania and depression scores, mediation analysis was used. The final mediation model is shown in supplementary Figure 1 below and total, indirect and direct effects results are shown in supplementary Table 1. The bias-corrected bootstrap of 95% confidence intervals show that the indirect effect of ECT on suicide via depression was significant (estimate = −0.230, 95%

Table 1
Comparison of Non-suicidal vs Suicidal patients with schizophrenia receiving ECT.

Total: 113	Non-Suicidal (Suicide scale 1 of 7) (N = 91) (N)	Suicidal (Suicide scale 2–7 of 7) (N = 22) (N)	P-value[1]
Gender (Female vs. Male)	46	10	0.790
Admission status (Voluntary)	28	12	0.036*
Clozapine use	20	7	0.331
Antidepressant use	19	14	<0.001*
Lithium use	2	9.1	0.116
Benzodiazepine use	44	2	0.366
Anticonvulsant use	19	5	0.849
Past ECT use	30	7	0.221
Bifrontal ECT	68	18	0.438
	Mean (SD)	Mean (SD)	P-value[2]
Age (years)	38.37 (14.37)	35.59 (16.01)	0.427
Number of ECT	9.74 (3.07)	10.18 (2.67)	0.532
Pre-ECT GAF	43.60 (6.14)	41.59 (5.85)	0.170
Pre-ECT MoCA	16.0 (10.8)	19.3 (8.9)	0.145
Post-ECT MoCA	18.9 (10.3)	20.9 (8.2)	0.416
Baseline Psychotic Subscale	13.0 (4.8)	13.7 (4.7)	0.548
Post ECT Psychotic Subscale	7.0 (3.5)	9.0 (4.0)	0.039*
Baseline Mania Subscale	6.8 (2.8)	6.0 (2.4)	0.241
Post ECT Mania Subscale	4.8 (1.4)	4.5 (0.7)	0.139
Baseline Depression Subscale	6.7 (3.1)	11.0 (3.5)	<0.001*
Post ECT Depression Subscale	5.4 (2.1)	7.0 (2.8)	0.003*

[1] = Chi-square test.
[2] = Independent t-test.

Table 2
BRPS Suicide Question Scores in patients with Schizophrenia receiving ECT.

	Non-suicidal group (N = 91)				Suicidal group (N = 22)			
	Baseline		Post-ECT		Baseline		Post-ECT	
Score	(N)	%	(N)	%	(N)	%	(N)	%
1	91	100	88	96.7	0	0	15	68.2
2	0	0	2	2.2	5	22.7	3	13.6
3	0	0	0	0	9	40.9	4	18.2
4	0	0	1	1.1	5	22.7	0	0
5	0	0	0	0	2	9.1	0	0
6	0	0	0	0	0	0	0	0
7	0	0	0	0	1	4.5	0	0

CI = −0.458 to −0.099). This means that the effect of ECT on suicide was significantly mediated by depression and suggests that the proportion of total effect (estimate= −0.319, 95% CI = −0.547 to −0.112) of ECT on suicide that was explained by depression was 72.2%.

4. Discussion

Our study shows that ECT reduces expressed suicidality in real world patients with Schizophrenia and that this decrease is largely due to a decrease in depressive symptoms. This decrease is rapid and occurs after about 10 sessions of ECT and within 2–3 weeks of starting ECT. Schizophrenia patients with higher BRPS depressive subscales (Togay et al., 2015), who have both insight and hopelessness (Pompili et al., 2007) or a history of suicide attempts, have a higher risk of future completed suicide (Kelly et al., 2004) and treatment resistance (Wimberley et al., 2016). The patients with suicidality did not differ from the non-suicidal patients in terms of severity of psychotic symptoms but had a higher average score on the Depressive subscale of BRPS of 11 (SD 3.5) (scale with a range from 4–28), compared to the non-suicidal group who scored 6.7 (SD 3.1). While these patients would be unlikely to qualify for a diagnosis of major depressive disorder (Hopko et al., 2001; Park et al., 2015), they still had measurable subsyndromal depressive symptoms, indicating the importance of assessing subsyndromal depressive symptoms in schizophrenia.

The decrease in expressed suicidality had little relationship to the improvement in positive psychotic symptoms in our sample, confirming earlier research that did not find a significant relationship between positive symptoms in schizophrenia and suicidality (Hawton et al., 2005). While the presence of psychotic symptoms such as command hallucinations has been associated with suicide in schizophrenia, they appear to only increase the risk in patients already predisposed to suicide. The strongest factors associated with suicide in schizophrenia are depressive disorder, previous suicide attempts and drug misuse (Hawton et al., 2005; Kasckow et al., 2011).

The only US FDA approved treatment to decrease suicidality in schizophrenia is clozapine (Hennen and Baldessarini, 2005; Meltzer et al., 2003). While other treatments for depression like SSRIs (Zisook et al., 2010) and psychotherapy (Mueser and Berenbaum, 1990) may be helpful in this regard, the evidence is inconclusive (Pompili et al., 2004). In depression, the gold standard for treatment of suicidality is ECT (Fink et al., 2014). However treatment guidelines for schizophrenia which purportedly draw from the same literature base differ in their recommendations depending on which side of the Atlantic ocean they are published (Dixon et al., 2009; Excellence and Britain, 2014). The APA Treatment guidelines for schizophrenia (Dixon et al., 2009) and Cochrane Review of ECT for schizophrenia (Tharyan and Adams, 2005) supports the use of ECT augmentation of pharmacotherapy in treatment resistant schizophrenia. However the UK NICE guidelines does not recommend the general use of ECT in the management of schizophrenia (Excellence and Britain, 2014). All the guidelines are silent on the use of ECT to treat suicidality in schizophrenia.

The main limitations of this study are the assessment of a complex construct (expressed suicidality) with a single response measure, and that the data analyzed were retrospectively collated from a clinical dataset. However, the latter is also a strength of the study, in that data were obtained in a real-world clinical setting from all patients in a clinical service, rather than a selected cohort electing to participate in research. Thus, the results of this study are more likely to be generalizable to other clinical settings. The small number of trained clinical raters assessing outcomes within an established framework (Martin et al., 2018) supports the reliability of the clinical dataset on which this study was based. We had small numbers of non-bifrontal ECT treatments (right unilateral and bitemporal) which precluded formal analysis of any potential differential effect of electrode placement on expressed suicidality in schizophrenia that could be present as

had previously been demonstrated in depression (Kellner et al., 2005; Prudic and Sackeim, 1999)

5. Conclusion

Suicidality in treatment resistant schizophrenia is a common and significant treatment challenge that may often be under-recognized and not specifically treated. This study demonstrates that ECT was effective in decreasing depression and expressed suicidality in patients with schizophrenia. Clinicians should consider the use of ECT as a treatment for managing suicidality and psychosis in patients with treatment resistant schizophrenia.

Author statement

All authors contributed equally to the data analysis and manuscript preparation. No funding was obtained for the study.

Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2020.112759.

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