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ORIGINAL PAPER

A novel seizure quality index based on ictal parameters for optimizing clinical decision-making in electroconvulsive therapy. Part 2: Validation

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Abstract
Early identification of patients who are at a high risk for an unfavorable outcome to ECT during the treatment course might be beneficial because it provides an opportunity for timely intensification or optimization of stimulus conditions. We aimed to validate a previously developed seizure quality index (SQI) that delivers a clinically relevant outcome prediction early in the treatment course and can be used within common clinical setting. Therefore, a prospective study was conducted. Patients ($n=26$) below the age of 65 years with a depressive episode and the clinical decision for ECT (right unilateral, brief pulse) were included and several ictal parameters, the SQI for non-response and non-remission, and the clinical outcome of the patients were documented. Logistic regression analysis revealed a statistically significant association between the SQI and non-response ($p=0.035$). A significant association between the clinical outcome of non-response and the classified outcome of non-response was detected ($p=0.041$). The overall classification accuracy regarding response/non-response was 71.3%, and the model revealed a sensitivity of 84.6% and a specificity of 61.5% for non-response. In this study, we could validate the SQI for the clinical outcome of non-response, but not for non-remission. Based on our data, the SQI might become an interesting clinical tool for early outcome prediction for ECT in patients with depression.

Keywords Electroconvulsive therapy · Depression · Outcome · Prediction

Introduction

Electroconvulsive therapy (ECT) is an effective and safe treatment option for specific forms of depression, such as treatment-resistant depression, psychotic depression, bipolar depression or depression in the elderly. Despite a remarkable efficacy even in highly treatment-resistant depression, there is still a considerable group of non-responders to ECT.

Although there are several demographic or clinical factors such as age, bipolarity, family history of depression, duration of current episode, history of medication failure in the current episode, episodic pattern, psychotic features or comorbid axis II disorder that might predict the contribution to the risk of non-response to ECT [1, 2, 9, 22], there has been less effort to extend our knowledge about predictive markers during the treatment course. Recently, we developed a seizure quality index (SQI) that predicts the risk of non-response and non-remission—at least for patients not older than 65 years—as early as after the second ECT session based on the extent of several ictal parameters of the seizure [11]. Those parameters are seizure duration measured by EMG, concordance as a surrogate of central inhibition, midictal amplitude, peak heart rate and hemispheric coherence. Unlike other ictal indices [6, 12, 13, 20, 23], our index forms an easy sum score, which could be reliably calculated at the bedside in convenience for the clinician, who needs to know, whether there is an increased risk for non-response for the patient.

In our previous study, that index was developed on a dataset and cross-validated by the leave-one-out method. In this second step, the aim was to validate the results of the SQI in an independent sample. The validation of the SQI that could predict the clinical outcome of

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non-response has direct and important clinical impact. Unlike demographic or clinical characteristics such as age or duration of the current depressive episode, it might be possible to modify these parameters within limits to improve the seizure quality and, therefore, to enhance the chance of a favorable clinical outcome.

Subjects and methods

Patients

Our prospective study has been approved by the appropriate ethics committee and was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from all participants before enrollment. The study took place from 2016 to 2018 at the Department of Psychiatry at the Central Institute of Mental Health in Mannheim, Germany. Inclusion criteria were a present depressive episode within the context of the diagnosis of either major depressive disorder or bipolar disorder (DSM-IV), age between 18 and 65 years, and the clinical decision for ECT. Exclusion criteria were substance-related disorders as the primary diagnosis, the lifetime diagnosis of schizophrenia and ECT within the past 6 months.

ECT treatment

Right unilateral brief pulse ECT was performed with a Thymatron IV device (Somatics, LLC. Lake Bluff, IL, USA). *S*-ketamine (~ 1.0 mg/kg) alone or in combination with propofol (both with ~ 0.5 mg/kg) or thiopental (~ 5 mg/kg) were used as anesthetic agents and succinylcholine (~ 1.0 mg/kg) for muscle relaxation. Seizure threshold was titrated at the initial session and stimulation dose at subsequent treatments was given at at least 2.5 times the seizure threshold [21, 24]. Charge was subsequently adjusted if seizures were considered as potentially insufficient during the ECT course (e.g. motor response time or EEG seizure activity < 15 s) [2]. ECT was continued until the subject showed either a remission or a stable response or did not show a significant response after at least 12 ECT sessions. Switch to bilateral stimulation was possible after at least six sessions with unilateral stimulation. No specifications on the concomitant psychotropic medication were made. ECT was continued until the subject showed either a remission or a stable response or did not show a significant response after at least 12 ECT sessions. In the case of no further and relevant clinical improvement for 2 weeks (4–6 ECT sessions), ECT was terminated.

Measures

Hamilton Depression Rating Scale (HDRS) score (21-item version) was assessed at baseline before the first ECT. Parameters documented for the second individual ECT session were: stimulation dose, (in mC), electrode placement (uni- or bilateral), type of narcotic agents (thiopental or *S*-ketamine), duration of the seizure measured by EMG (in seconds), concordance (EMG seizure duration/EEG seizure duration), midictal amplitude (in mV), peak heart rate (as beats per minute; bpm) and interhemispheric coherence (in %). The values for midictal amplitude, peak heart rate and interhemispheric coherence were produced by the built-in algorithm of the ECT device. To optimize accuracy, in all sessions baseline recordings prior to ECT were performed and relevant artifacts were eliminated. At the end of the treatment course, the following data were recorded: final HDRS score (within 1 week after the last ECT session), number of ECT sessions needed, non-response to treatment (defined as less than 50% reduction of baseline HDRS score) and non-remission to treatment (defined as a final HDRS score > 10, as used in the consortium for research in ECT (CORE) studies [5]). The rater for the depressive psychopathology (LK) was blinded concerning ictal parameters and the prediction of the SQI from the second ECT session.

SQI

The SQI for non-response and the SQI for non-remission are derived from the values from those five ictal parameters [11]. For each ictal parameter (ictal duration measured by EMG, concordance, peak heart rate, midictal amplitude and interhemispheric coherence), a cut-off value for non-response and for non-remission was calculated. The ictal parameters from the second ECT session was used for the prediction (Table 1). For each ictal parameter, whose value was above that cut-off point, one point could be added to the SQI sum score. Thus, the SQI could lie between zero and five points. Non-response and/or non-remission are predicted in cases where the sum score is below three points.

Statistical analyses

Unpaired *t* tests and chi-square tests were used to examine differences in demographic and clinical characteristics between two groups of patients (non-responders with responders, non-remitters with remitters, validation sample with training sample), with which the SQI was developed. The impact of the ECT treatment on changes of the HDRS score was analyzed with a paired *t* test. The association between the clinical outcome and the classified outcome

Table 1 Summary of the seizure quality index (SQI) for non-response and for non-remission for the group of non-geriatric adults below the age of 65

Parameters	Points to acquire	Outcome	
		Non-response	Non-remission
Seizure duration by EMG	1	≤30 s	≤55 s
Concordance	1	≤0.70	≤0.70
Midictal amplitude	1	≤200 mV	≤215 mV
Peak heart rate	1	≤150 bpm	≤155 bpm
Interhemispheric coherence	1	≤98%	≤98%
Σ	0–5	≤2: prediction for non-response/non-remission >2: prediction for response/remission	

All parameters were derived from the second ECT session

was performed with Fisher's exact test. Logistic regression analyses were applied to test for the association between the SQI and the outcome variables of non-response and non-remission. Receiver operating characteristic curve (ROC) analyses were used to assess the diagnostic efficiency of the SQI with respect to the criteria response/non-response and remission/non-remission. Statistics were performed using STATA® (StataCorp, Texas 77845, USA, version 11) at a significance level ≤0.05 (two-tailed).

Results

We included 26 patients between the age of 18 and 65 with a full data set and a completed course of ECT into our validation study. Detailed demographic and clinical features of the participants are shown in Table 2 and treatment parameters in Table 3.

In general, ECT was effective with a reduction of the mean initial HDRS from 27.5 ± 6.9 to 12.2 ± 7.0 after the final session ($p < 0.001$). Thirteen (50.0%) patients had to be considered as "non-responders", whereas the other 13 patients were considered as "responders". 16 patients (61.5%) had to be considered as non-remitters, whereas ten patients (38.5%) fulfilled the definition of a full remission.

53.9% ($n = 14$) received *S*-ketamine alone as intravenous anesthetics, whereas 23.1% ($n = 6$) received *S*-ketamine in combination with propofol, and another six patients received thiopental for anesthesia during ECT. The type of usage of anesthesia was neither associated with non-response ($p = 0.32$) nor non-remission ($p = 0.18$). 23.1% ($n = 6$) of the patients were switched to bilateral stimulation after at least six sessions with right unilateral stimulation due to

Table 2 Demographic and clinical features of all patients and the comparison of groups with different clinical outcomes

	All subjects	Responders	Non-responders	Statistics (responders vs. non-responders)	Remitters	Non-remitters	Statistics (remitters vs. non-remitters)
Number of subjects	26	13 (50.0%)	13 (50.0%)	–	10 (38.5%)	16 (61.5%)	–
Age, mean ± SD in years (min–max)	45.6 ± 12.7	44.2 ± 12.9	47.1 ± 12.9	$p = 0.57$	45.5 ± 13.8	45.7 ± 12.4	$p = 0.97$
Sex female *n* (in %)	17 (65.4)	8 (61.5)	9 (69.2)	$p = 0.68$	7 (70.0)	10 (62.5)	$p = 0.70$
Type of depression: unipolar *n* (in %)	19 (73.1)	9 (69.2)	10 (76.9)	$p = 0.66$	7 (70.0)	12 (75.0)	$p = 0.78$
Personality disorder (yes in %)	12 (46.2)	5 (38.5)	7 (53.9)	$p = 0.43$	3 (30.0)	9 (56.3)	$p = 0.19$
Mood stabilizer intake during ECT (yes in %)	19.2	30.8	7.7	$p = 0.32$	20.0	18.8	$p = 0.99$
Lithium intake during ECT (yes in %)	26.9	15.4	38.5	$p = 0.38$	20.0	31.3	$p = 0.67$
Antipsychotics intake during ECT (yes in %)	73.1	92.1	53.9	$p = 0.073$	90.0	62.5	$p = 0.19$
Antidepressant intake during ECT (yes in %)	50.0	46.2	53.9	$p = 0.99$	40.0	56.3	$p = 0.69$
Benzodiazepine intake during ECT (yes in %)	50.0	53.9	46.2	$p = 0.99$	60.0	43.8	$p = 0.69$

Table 3 Comparison of the general treatment effects and all single ictal parameters of the second ECT session (mean ± SD)

	All subjects	Responders	Non-responders	Statistics	Remitters	Non-remitters	Statistics
Number of subjects	26	13 (50.0%)	13 (50.0%)	–	10 (38.5%)	16 (61.6%)	–
HDRS, sum score							
Baseline HDRS	27.5 ± 6.9	28.3 ± 7.7	26.7 ± 6.2	$p = 0.56$	26.5 ± 7.1	28.1 ± 6.9	$p = 0.57$
Final HDRS	12.1 ± 6.5	7.5 ± 4.9	16.8 ± 4.1	$\mathbf{p < 0.001}$	5.4 ± 2.4	16.3 ± 4.2	$\mathbf{p < 0.001}$
Numbers of ECT sessions	13.9 ± 5.9	12.7 ± 5.1	15.4 ± 6.8	$p = 0.28$	12.4 ± 5.4	15.0 ± 6.2	$p = 0.31$
Mean stimulus dose	29.0 ± 13.0	26.5 ± 13.6	31.5 ± 12.3	$p = 0.34$	29.4 ± 14.8	28.9 ± 12.6	$p = 0.93$
Seizure duration by EMG in s	32.2 ± 16.2	34.6 ± 17.1	29.8 ± 15.6	$p = 0.48$	31.9 ± 16.1	32.4 ± 16.9	$p = 0.94$
Concordance	0.66 ± 0.25	0.69 ± 0.25	0.63 ± 0.26	$p = 0.56$	0.67 ± 0.26	0.66 ± 0.25	$p = 0.87$
Midictal amplitude in mV	181.4 ± 73.7	202.1 ± 54.9	160.8 ± 85.9	$p = 0.16$	202.5 ± 62.5	168.3 ± 78.9	$p = 0.26$
Peak heart rate in bpm	129.0 ± 24.7	130.8 ± 31.7	127.6 ± 16.0	$p = 0.75$	131.1 ± 30.7	128.0 ± 21.1	$p = 0.76$
Coherence in %	94.3 ± 8.7	97.1 ± 2.4	91.3 ± 11.9	$p = 0.10$	96.9 ± 2.5	92.5 ± 10.9	$p = 0.23$
Seizure quality index (SQI)	–	2.31 ± 1.2	1.15 ± 1.3	$\mathbf{p = 0.025}$	1.70 ± 1.1	1.00 ± 1.0	$p = 0.11$

Bold text highlights statistical significance ($p < 0.05$)

p values refer to *t* tests comparing responders with non-responders and remitters with non-remitters

non-response to ECT at that point. Of these six patients, three (50.0%) and one (16.7%) were considered as responders and remitters, respectively, at the end of the treatment.

The variable age was neither related to the clinical outcome of non-response ($p = 0.88$) nor to non-remission ($p = 0.97$), and negatively correlated only with the ictal parameter "midictal amplitude" ($F(1,24) = 4.6$, $p = 0.043$), but not with any other ictal parameters from which the SQI were derived. Age was not associated with the SQI itself for non-response ($p = 0.23$) and non-remission ($p = 0.26$) in this sample of patients with the age under 65.

Comparison with training sample

The patients from the present validation sample were all treated at the same site with similar treatment conditions as the patients from the previous training sample with whom the development of the SQI was performed. Consistent with that, no differences between these two samples could be found for any of the following demographical and clinical data: age (45.6 vs. 45.3 years; $p = 0.93$), sex (65.4% female vs. 54.4%; $p = 0.49$), percentage of comorbid personality disorders (46.2% vs. 32.6%; $p = 0.31$), type of depression (73.1% unipolar depression vs. 82.6%, $p = 0.38$). No group differences could be detected for both, the initial HDRS score (27.5 vs. 27.7; $p = 0.96$) and that after ECT (12.1 vs. 11.2; $p = 0.43$) did not differ from each other.

Compared to the training sample, the present sample showed a significant higher percentage of non-response (50.0% vs. 21.7%, $p = 0.014$), but no difference for non-remission (61.5% vs. 52.2%; $p = 0.44$). The reduction of the HDRS points was similar in both groups (15.2 vs. 16.5 points; $p = 0.48$). The number of individual ECT sessions were higher in the current validation sample than from the previous study (13.9 vs. 11.6, $p = 0.024$). Switch to bilateral stimulation due to non-response to right unilateral stimulation was performed in 23.1% compared to 23.9% ($p = 0.99$).

SQI validation

Outcome of non-response

The SQI was lower in non-responders (1.15 ± 1.3) compared to those patients, who did show a response to the treatment (2.31 ± 1.2). 11 out of 13 non-responders (84.6%) were identified correctly by the SQI as early as on the second ECT session. A significant association between the clinical outcome of non-response and the classified outcome of non-response was detected (Table 4; $p = 0.041$). From the responders, eight (61.5%) subjects were classified correctly (Table 4). The overall classification accuracy was 71.3%. Thus, the model revealed a sensitivity of 84.6% (95% CI 54.6–98.1), and a specificity of 61.5% (95% CI 31.6–86.1) for non-response.

A binomial logistic regression was performed to ascertain the effects of the SQI on the probability that the subject showed a non-response. The logistic regression analysis examining the effect of the SQI on the probability of non-response revealed a statistically significant effect

Table 4 Contingency table for the actual clinical outcome (non-response and response) and the classified outcome by the SQI

	Classified as		
	Non-response	Response	
Non-response	11(84.6%)	2 (15.4%)	13 (100%)
Response	5 (38.5%)	8 (61.5%)	13 (100%)

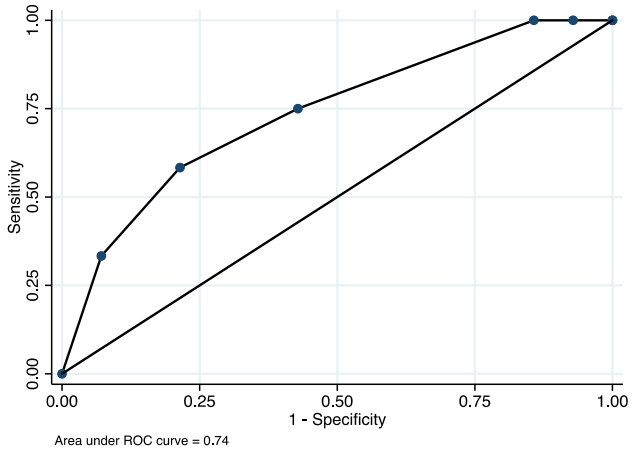

Fig. 1 ROC curve analysis for predicting "non-response" from the SQI

Table 5 Contingency table for the actual clinical outcome (non-remission and remission) and the classified outcome by the SQI

	Classified as		
	Non-remission	Remission	
Non-remission	14 (87.5%)	2 (12.5%)	16 (100%)
Remission	7 (70.0%)	3 (30.0%)	10 (100%)

($\chi^2 = 5.3$, $p = 0.035$, Nagelkerke pseudo $R^2 = 0.245$). ROC curve analysis for predicting non-response showed an AUC 0.74 (Fig. 1).

Outcome of non-remission

The SQI did not differ significantly in patients with a non-remission (1.0 ± 1.0) compared to the remitters (1.7 ± 1.1; $p = 0.11$). The SQI was able to identify 14 from the 16 patients (87.5%) who were considered as non-remitters. For remission, SQI identified only three from ten patients correctly (30.0%). The overall classification accuracy is 65.4%. Thus, the model for non-remission revealed a sensitivity of 87.5% (95% CI 61.7–98.4) and a specificity of 30.0% (95% CI 6.7–65.2). No association between the clinical outcome of non-remission and the classified outcome of non-remission was found (Table 5; $p = 0.34$).

A binomial logistic regression was performed to test the effects of the SQI on the probability that the subject showed non-remission. The logistic regression analysis examining the effect of the SQI on the probability of non-remission revealed no statistically significant effect ($\chi^2 = 2.7$, $p = 0.011$). ROC curve analysis for predicting non-remission showed an AUC 0.69.

Discussion

The seizure quality index (SQI) that could be built after the second ECT session was validated for the prediction of non-response to ECT in patients not older than 65 years with depression. A significant association between the clinical outcome non-response and the classified outcome of non-response, and a significant effect of the SQI on the probability of non-response could be shown, whereas no such associations were found for non-remission.

In general, we were able to replicate those results we got from the initial sample. ECT is highly effective, that is why the focus of this index is on detecting non-response and non-remission. Therefore, the results with identifying 84.6% of those non-responders (and 87.5% for non-remitters) are promising. For comparison, the results from our previous study were 87.2% for non-response and 50.0% for non-remission [11]. Thus, the SQI could be considered as validated for non-response, but not for non-remission. This validation adds more evidence to the usefulness of the SQI, which has the advantages that it is easy to calculate and highly applicable for the use within the clinical context—at least in those setting, where at the beginning of an ECT course similar stimulation parameters are used (RUL, brief pulse, stimulation moderately above seizure threshold). The next step has to be the evaluation if in cases where a unfavorable outcome is predicted early during ECT could be prevented by intensifying the treatment early on with procedures such as switching to bilateral stimulation, enhancing the stimulus dose or changing the anesthetic agent [15, 16].

There was a significant higher percentage of non-response in the present sample, compared to the training sample, which could not be easily explained by demographic or clinical differences between those samples. However, the mean extent of HDRS reduction during ECT did not differ in both sets; thus beyond a mere power problem in this second sample, the relative arbitrariness of the response definition of 50% HDRS reduction might explain this discrepancy.

The SQI for non-remission could not be validated in that manner such as the SQI for non-response. Most likely, a type II error could be assumed due to the small sample size ($n = 26$). Additionally, the outcome "remission" seems more arbitrary than "response". In accordance to this, there is an on-going discussion, which outcome parameter could be more of use in ECT [18, 19] and which cut-off value should be used [27]. In our study, we used the definition of the CORE studies; however, a cut-off of ≤ 7, often used in pharmacotherapy studies [3, 7, 8, 25, 26], would have been similarly plausible and would have revealed at least a result at trend level significance ($\chi^2 = 3.3$; $p = 0.085$).

The SQI for non-response is clinically relevant, especially due to its high predictive power obtainable early

during a course of ECT. This allows for a timely modification or intensification of treatment in such cases where non-response might become an issue. This could be done by increasing the stimulation or pulse width, intensity, switching to bilateral stimulation [14] or switching to a narcotic agent with less anticonvulsive properties such as ketamine or etomidate [10]. Of course, it must be emphasized that the clinical decision to modify treatment conditions must not be based entirely on such an index, but the individual situation of each patient and the experience of the clinician should be considered, too.

The major limitation of the present study is that the choice of dosing at at least 2.5 times the seizure threshold is seen as a suboptimal treatment technique by some authors [4, 17]. It could be argued that the relatively low response and remission rates, and the high number of ECT sessions in each patient in our study is due to that low dosing regime. However, a dosing at at least 2.5 times the seizure threshold is defined as "moderate" and recommended in the current edition of the guideline of the American Psychiatric Association (APA; The Practice of Electroconvulsive Therapy) [2]. It should be noted, that the dosing regime in this study did not differ from those in the previous study, in which the SQI was developed and where the response and remission rates were within very reasonable ranges (88.4% response rate and 64.0% remission rate). It should be explored in further studies, whether a similar SQI could be established for higher suprathreshold stimulations and/or bilateral stimulation, for which our current model is not suitable yet. However, this applies only for the calculation of the SQI in the second session. Any modification of the parameters after that session was and is possible. Another limitation of our study is its monocentric design. Therefore, local circumstances might have biased the results and limits generalizability. There might also have been occurred a power problem due to the low sample size. We are aware that other ECT devices provide different information about the seizure than the ECT device used throughout our study (Thymatron IV, Somatics, LLC. Lake Bluff, IL, USA): parameters, such as peak heart rate or interhemispheric coherence are either not provided or are defined or measured differently. Similar as in the study in which the index was developed, concomitant medication was allowed, but it already has been shown in that previous study, that neither the intake of lithium, nor antipsychotics, nor mood stabilizers had a significant impact on the single ictal parameters or the SQI itself. However, the relatively high intake of concomitant psychotropic medication might be one reason for the high number of individual ECT sessions. Beneath exploring the validity and clinical benefit of the SQI in different stimulation paradigms, future studies with a higher sample size should explore whether the SQI could be combined with demographic or clinical data to improve its value. Additionally, associations with biomarkers, such as brain-derived neurotropic factor and other hormones or immunological markers, should be tested.

Conclusions

To conclude, our study provides promising data about the prediction of ECT response at an early stage, but only for limited stimulation conditions (RUL, brief pulse, stimulation 2.5 times above seizure threshold, patients with major depressive episodes). We hope to have made a useful contribution with the validation of the SQI for non-response for the aim to early identify those patients, who have a considerable high risk of an unfavorable outcome.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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