Severe Postictal Confusion After Electroconvulsive Therapy
A Retrospective Study

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Objectives: Severe postictal confusion (sPIC) is an important but poorly investigated adverse effect of electroconvulsive therapy (ECT). In this retrospective study, prevalence of sPIC and potential risk factors were explored.

Methods: Medical charts of 295 ECT patients (mean ± SD age, 57 ± 15 years; male, 36%) were scrutinized for occurrence of sPIC, as well as demographic, clinical, and treatment characteristics. Patients showing sPIC were compared with patients who did not, using univariate statistics. Multivariate analyses with a split-sample validation procedure were used to assess whether predictive models could be developed using independent data sets.

Results: O 295 patients, 74 (25.1%) showed sPIC. All patients showing sPIC needed extra medication, 9% (n = 7) required physically restraints, and 5% (n = 4) had to be secluded. Univariate analyses showed several trends: patients with sPIC were more often males ($P = 0.05$), had more often history of cerebrovascular incident ($P = 0.02$), did not use concomitant selective serotonin reuptake inhibitors ($P = 0.01$), received higher median dosage of succinylcholine ($P = 0.02$), and received pretreatment with flumazenil more often ($P = 0.07$), but these associations did not remain significant after correction for multiple comparisons. Multiple logistic regression analysis did not result in a model that could predict sPIC in the holdout data set.

Conclusions: In this retrospective naturalistic study in 295 ECT patients, the prevalence of sPIC appeared to be 25%. Patients showing sPIC were characterized by male sex, history of cerebrovascular incident, use of higher-dose succinylcholine, and pretreatment with flumazenil. However, multivariate analysis revealed no significant model to predict sPIC in independent data.

Key Words: electroconvulsive therapy, severe postictal confusion, predictors, adverse effects

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Electroconvulsive therapy (ECT) is an effective and safe treatment for several severe psychiatric disorders, such as therapy-resistant depression, psychotic depression, catatonia, and schizophrenia.[1,2] An important adverse effect of ECT is postictal confusion, which is a state of disorientation, confusion, decrease of consciousness, agitation, and/or motoric unrest.[3] Most often, these symptoms are mild. However, severe postictal confusion (sPIC) occurs in 16% to 39.9% of ECT patients.[4–6] Severe postictal confusion may lead to injuries in the patient and surroundings, making this a very stressful event, not only for patients but also for family and health care professionals involved. After experiencing sPIC, most patients experience feelings of shame and/or anticipation fear for future ECT sessions, which sometimes leads to prematurely discontinuation of the ECT course.[3,7,8]

Studies regarding prevalence and risk factors of sPIC are sparse.[7] In a systematic review of 43 studies, no significant risk factors for sPIC were found, possibly because of methodological shortcomings, small sample sizes, heterogeneity in study design, and the used definition of sPIC.[7] However, nonsignificant associations were suggested between sPIC and catatonic symptoms, cerebrovascular accident (CVA), Parkinson' disease, dementia, bilateral (BL) electrode placement, and longer seizure duration. Also, in retrospective studies, the concomitant use of quetiapine, lithium carbonate, and antidepressants during ECT was described as potential risk factor.[9,10] Other studies focused on possible treatments of sPIC and suggested preventive effects of olanzapine,[8] dexmedetomidine,[7,11] and anticholinergic medication.[7,12] More knowledge about sPIC in ECT, especially regarding prevalence, risk factors, and preventive strategies, is essential to improve patient care.

In this retrospective study, we explored in a naturalistic, nonselected cohort of ECT patients: (1) the prevalence of sPIC, (2) clinical and treatment characteristics and interventions that were needed to handle the sPIC, and (3) potential independent risk and preventive factors for sPIC.

MATERIALS AND METHODS

Study Population and Setting

This single-center study was conducted at the department of psychiatry, Rijnstate hospital, Arnhem, The Netherlands, which serves as a 31-inpatient-bed unit, specialized in ECT for treatment-resistant mood disorders and catatonia, with a catchment area of 650,000 inhabitants. For this study, the Dutch Central Committee on Research Involving Human Subjects confirmed that written informed consent was not required, because patients were not actively involved and not exposed to experimental interventions (CCMO-number, 2020-6879). Data were extracted from the electronical medical records (EMRs) of all patients who received at least 4 ECT sessions in the period between January 2012 (ie, introduction of EMRs in the hospital) and August 2020. Patients were excluded if they had incomplete EMRs or when the ECT course was still in progress (eg, continuation ECT). After extraction, all included data were completely anonymized before further analyses.

Definition of sPIC

To be identified as a patient with sPIC, in advance, the following 2 inclusion criteria were defined: (1) the patient had shown documented disturbing behavior (ie, nonpurposeful movement, severe restlessness, aggression, removal of tubes, and violence), developed within 4 hours after an ECT session, for which direct medical interventions were required (ie, administration of extra sedatives, application of constraints, and/or other restrictions), and (2) these interventions were not the result of other medical

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problems, such as prolonged seizure duration or prolonged apnoea. Patients were included when both criteria were met.

Included Variables

Subsequently, EMRs were scrutinized for descriptions of the inclusion criteria. Demographic and clinical characteristics were registered, such as age, sex, primary psychiatric diagnosis, presence of catatonic and psychotic features, psychiatric and somatic comorbidity (including history of CVA), cerebral abnormalities on magnetic resonance imaging (MRI) scans (if available, described by radiologists and within 1 year before the start of the ECT course), and concomitant medication use. Dosages of medication were converted into 1 dosage equivalent (if possible), for selective serotonin reuptake inhibitors (SSRIs) in fluoxetine equivalents,[13] for antipsychotics in haloperidol equivalents,[14] for benzodiazepines in diazepam equivalents,[15] and for opioids in morphine equivalents.[16] Polypharmacy was defined as the use of more than 5 different medications within 24 hours before an ECT session. Furthermore, relevant ECT characteristics, such as electrode placement, ECT dosage method, applied electrical dose, pulse width, dosage of etomidate and succinylcholine, flumazenil usage, electromyographic (EMG) and electroencephalographic (EEG) seizure durations, and total ECT sessions in the course, were collected.

For quantification of the severity of the depressive episode, the Hamilton Depression Rating Scale (HDRS)[17] and Montgomery-Åsberg Depression Rating Scale[18] were used. For cognitive functioning, Mini-Mental State Examination[19] and Montreal Cognitive Assessment[20] were used. Mood and cognitive functioning scores were only included, if assessed within 1 month before and 1 month after the ECT course. Mood scores were converted into HDRS equivalents[21] and cognition scores into Mini-Mental State Examination equivalents.[22] Response was defined as ≥50% decrease of HDRS equivalents compared with baseline scores, and remission was defined as HDRS equivalent score of ≤7 after the ECT course.

In addition, more specific data of patients showing sPIC were scrutinized, such as number of previous ECT courses, number of the ECT session after which sPIC first occurred, several ECT parameters at this session, and concomitant medication use and its dosage. Finally, pharmacological interventions used to handle the sPIC and the use of restraints and other restrictions (ie, transference to closed ward or seclusion room) were extracted from the EMR.

ECT Procedure

All patients received treatment according to the Dutch clinical guidelines on ECT. Anesthesia was mostly induced intravenously with etomidate (0.2–0.3 mg/kg body mass) and muscle paralysis with succinylcholine intravenously (0.5–1 mg/kg body mass). Appropriate oxygenation (100% oxygen, positive pressure) was provided until spontaneous resumption of breathing. A constant current (900 mA), brief pulse (0.5–1.0 ms) ECT stimulation was administered using Thymatron System IV (Somatics Incorporation, Lake Bluff, IL). Electrode placement was either BL, left unilateral, or right unilateral (RUL) according to d'Elia, as was decided by the treating psychiatrist based upon the clinical condition or previous experience in that particular patient. Seizure duration was measured as visual motor activity at a cuffed limb (EMG) and with EEG output of the ECT device. Regular ECT-dosage methods were used, such as (half) age-based method and dose-titration method. A motor seizure duration of at least 20 seconds was regarded as adequate. If dose-titration method was used, therapeutic ECT dose was set at 2.5 times seizure threshold for BL and 6 times seizure threshold for RUL position. Further dosage was determined by the quality of the seizure and the clinical effectiveness. Depending on the psychiatrist's decision, 0.5 mg of flumazenil would be administered intravenously shortly before the ECT stimulus to antagonize concomitant used benzodiazepines.

Statistical Analyses

Data were analyzed using frequentist statistics in SPSS for Windows, version 26 (SPSS Inc, Chicago, IL).

Descriptive Statistics

Categorical variables were calculated as frequencies and percentages, whereas continuous variables were calculated as mean and SD; if normally distributed, median and interquartile range (IQR) were used in nonnormally distributed variables.

Univariate Statistics

First, patients who showed sPIC were compared with patients without sPIC across the entire cohort. Univariate analyses were used to explore any differences between the 2 groups; categorical variables were compared using χ^2 tests or Fisher exact tests, normally distributed continuous variables were compared using independent 2-sided *t* tests, and nonnormally distributed variables were compared with Mann-Whitney *U* tests. Bonferroni correction was applied to correct for the multiple comparisons between groups.

Multivariate Statistics

To explore possible independent predictors of occurrence of sPIC, multivariate logistic regression models were built using "occurrence of sPIC" as a dependent variable and a maximum of 7 independent variables.[23] To examine the most proper model, we used several steps in these analyses. First, the cohort was split into 2 groups: a training set containing two thirds of the cohort (n = 191) and an independent test set containing the other third (n = 104). Division of sets was at random, except for "occurrence of sPIC" to guarantee a prevalence of 25% in both sets. In the training set, all previous univariate analyses were repeated. Subsequently, variables showing differences with $P \leq 0.1$ (without Bonferroni correction) in the univariate analyses were used to build a multivariate logistic regression model, which was then applied to the independent test set. Second, this procedure was repeated with the cohort being split in an equal ratio (ie, training set of n = 153 [52%] and test set of n = 141 [48%]) to explore whether this would result in comparable independent predictors. Finally, Lasso regularization was used in the training-set model to reduce the risk of overfitting by inducing sparsity in the number of predictors.

RESULTS

Prevalence, and Clinical and Treatment Characteristics

Included Sample

In the period January 2012 to August 2020, 388 patients were treated with ECT at Rijnstate hospital. Data from 93 patients (24%) had to be excluded (ie, incomplete EMRs [n = 49], ongoing ECT course [n = 35], and <4 ECT sessions registered [n = 9]), resulting in a total sample of 295 patients eligible for inclusion. A total of 4982 ECT sessions were scrutinized for the occurrence of sPIC.

Prevalence of sPIC

In these 295 patients, 74 patients (25.1%) showed sPIC at least at 1 ECT session during the treatment course. Mostly, sPIC occurred after the first ECT session (n = 27 [35.1%]; Fig. 1). In 63 of the 74 patients (85%), sPIC was seen within the first 5 ECT sessions.

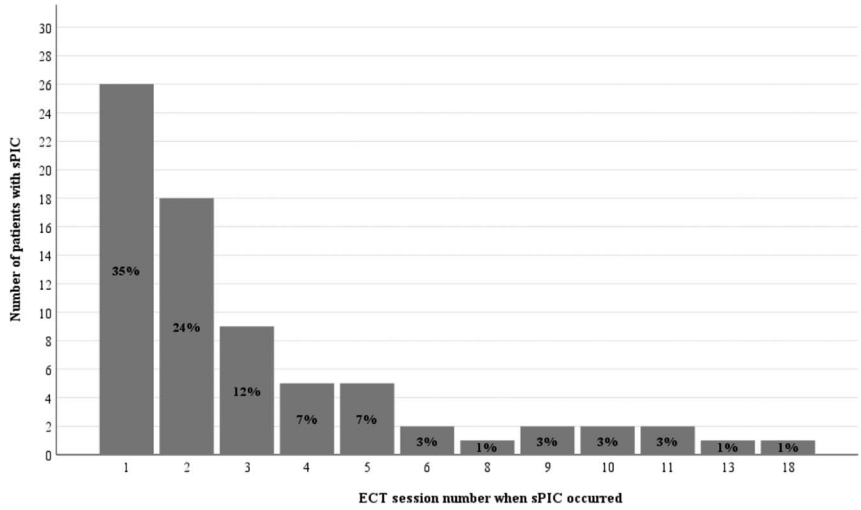

FIGURE 1. Bar chart showing the ECT session number at which sPIC first occurred; in 85% of patients (n = 63 of 74), sPIC occurred within the first 5 ECT sessions. full color online

Demographic and Clinical Characteristics

In Table 1, demographic and clinical characteristics of the total sample (n = 295) and patients showing sPIC (n = 74) as those without sPIC (n = 221) are summarized. Mean ± SD age was 57 ± 16 years, and 36% (n = 106) of the included ECT patients was male. Most patients were treated for unipolar depressive disorder (n = 209 [71%]), and 47 (16%) showed catatonic features. Ten patients (3%) had a history of CVA, and in 165 patients, cerebral MRI scans were available showing abnormalities in 37.6% (n = 62; ie, atrophy [n = 32 (20%)], ischemic damage [n = 4 (2%)], and white matter lesions [n = 52 (32%)]). Of the total sample, 121 patients (41%) used concomitant antidepressants during the ECT course, of which 20 (7%) used an SSRI. Mood scores at baseline and after the ECT course were available in 152 patients, showing that median HDRS equivalent before ECT was 25 (IQR, 20–29) points and 11.5 points after the ECT course (IQR, 6.0–16.5; mean improvement, 12.2 ± 9.4 points; Wilcoxon signed rank test; $Z = -7.56$, $P < 0.001$).

Treatment Characteristics

Median doses of used etomidate and succinylcholine were 20.0 mg (IQR, 16.0–20.0 mg) and 75 mg (IQR, 75–100 mg), respectively. Flumazenil was administered in 28% (n = 83) of patients. At the start of the ECT course, mostly BL electrode position (n = 169 [57%]) was applied. In all other cases, RUL electrode position was the position of choice (n = 126 [43%]). Median electrical dose was 202 mC (IQR, 151–277 mC). The median seizure EEG duration was 67 seconds (IQR, 49–86 seconds), and median EMG duration was 44 seconds (IQR, 34–59 seconds).

Comparison Between sPIC and Non-sPIC Groups

Demographic and Clinical Characteristics

In the sPIC group (n = 74), more men (n = 34 [46%]) were present compared with the non-sPIC group (ie, 72 of 221 patients [33%]; $\chi^2_2 = 3742$, $P = 0.05$; Table 1). Psychiatric diagnoses did not differ between groups. Patients with sPIC showed more often (n = 6 [8%]) a history with a cerebrovascular incident (CVA) than patients without sPIC (n = 4 [2%]; Fisher exact test, $P = 0.02$). Concomitant medication use did not differ between groups, except that none of patients showing sPIC used SSRIs versus 20 patients (9%) in the non-sPIC group (Fisher exact test, $P = 0.01$). Mood severity and cognitive functioning scores at baseline did not differ between groups. None of the univariate results remained significant after Bonferroni correction (Table 1).

Treatment Characteristics

A higher dose of succinylcholine was administered to patients showing sPIC (median: 100.0 mg [IQR, 75.0–100.0 mg; n = 70] vs median: 75.0 mg [IQR, 75.0–100.0 mg; n = 211]; Mann-Whitney *U* test, 6765; $Z = -2.25$; $P = 0.02$). Use of flumazenil was more frequent in patients showing sPIC at trend level (35% [n = 26] vs 26% [n = 57]; $\chi^2_2 = 3392$, $P = 0.07$). Electrode placements did not show differences between groups ($P = 0.98$), as well as medians of the administered electrical dose ($P = 0.75$) and of the seizure durations on EMG and EEG ($P = 0.55$ and $P = 0.75$, respectively). The applied ECT-dosage method did not differ between groups ($P \geq 0.69$). Again, none of the univariate results remained significant after Bonferroni correction.

Potential Risk Factors for sPIC

Multiple steps were applied to build a predictive model after dividing the data in a training and test set (with a ratio of 2:1). In the training set (n = 191), the following variables showed differences between groups with *P* values of ≤0.1 (without Bonferroni correction): male sex, presence of bipolar depression, presence of catatonic features, history of CVA, use of concomitant SSRI, dose of succinylcholine, and pretreatment with flumazenil. Logistic regression analysis confirmed that these variables together could predict sPIC in the training set ($\chi^2_7 = 23.9$, $P = 0.001$). However, the Omnibus test using these same variables appeared not significant in the test set (n = 104; $\chi^2_7 = 8.44$, $P = 0.295$), indicating that this model did not make a better prediction than the model without these variables. Because the lack of generalization to the test set may reflect overfitting of the model on the training set, we subsequently used Lasso regularization to induce sparsity in the multivariate training-set model. This method did not yield any variables in the training set that were eligible for a predictive model.

TABLE 1. Demographic, Clinical, and Treatment Characteristics of Patients Receiving ECT, Who Have Shown sPIC Compared With Those Who Did Not Show sPIC

	Total Sample (n = 295)	Patients Without sPIC (n = 221)	Patients With sPIC (n = 74)	*P*
Demographic characteristics				
Age at first ECT, mean ± SD, y	57.3 ± 15.5	57 ± 16	57 ± 13	0.95*
Male sex, n (%)	106 (36)	72 (33)	34 (46)	**0.05**†
Clinical characteristics				
Primary diagnosis for ECT				
Unipolar depression, n (%)	209 (71)	157 (71)	52 (70)	1.00†
Bipolar depression, n (%)	45 (15)	30 (14)	15 (20)	0.23†
Schizoaffective depression, n (%)	16 (5)	12 (5)	4 (5)	1.00‡
Schizophrenia and other psychosis, n (%)	6 (2.3)	6 (2.5)	0	1.00‡
Presence of psychotic features, n (%)	128 (43)	93 (42)	35 (47)	0.52†
Presence of catatonic features, n (%)	47 (16)	40 (18)	7 (10)	0.12†
Comorbid psychiatric diagnoses, n (%)	111 (38)	84 (38)	27 (37)	0.92†
+Comorbid somatic diagnoses, n (%)	214 (73)	160 (72)	54 (73)	1.00†
History of CVA, n (%)	10 (3)	4 (2)	6 (8)	**0.02**‡
Presence of dementia, n (%)	5 (2)	4 (2)	1 (1)	1.00‡
Presence of Parkinson's disease, n (%)	5 (2)	4 (2)	1 (1)	1.00‡
MRI scan of cerebrum available, n (%)	165 (56)	122 (55)	43 (58)	
Presence of any abnormality, n (%)	62 (38)§	43 (35)§	19 (44)§	0.39†
Presence of cerebral atrophy, n (%)‖	32 (20)§	25 (21)§	7 (17)§	0.75†
Presence of recent cerebral ischemic damage, n (%)¶	4 (2)§	3 (3)§	1 (2)§	1.00‡
Presence of cerebral white matter lesions, n (%)	52 (32)§	35 (29)§	17 (40)§	0.26†
Concomitant medication use during ECT course				
Antidepressants, n (%)	121 (41)	90 (41)	31 (42)	0.90†
SNRI, n (%)	12 (4)	8 (4)	4 (5)	0.50‡
SSRI, n (%)	20 (7)	20 (9)	0	**0.01**‡
TCA, n (%)	84 (29)	60 (27)	24 (33)	0.35†
Other, n (%)	4 (1)	2 (1)	2 (3)	0.26‡
Mood stabilizing drugs, n (%)	32 (11)	21 (10)	11 (15)	0.27†
Lithium carbonate, n (%)	14 (5)	9 (4)	5 (7)	0.35‡
Valproic acid, n (%)	10 (3)	8 (4)	2 (3)	1.00‡
Lamotrigine, n (%)	5 (2)	3 (1)	2 (3)	0.60‡
Carbamazepine, n (%)	3 (1)	1 (0.5)	2 (3)	0.15‡
Antipsychotics, n (%)	182 (62)	137 (62)	45 (61)	1.00†
Haloperidol, n (%)	40 (14)	28 (13)	12 (16)	0.54†
Quetiapine, n (%)	52 (18)	43 (20)	9 (12)	0.23†
Olanzapine, n (%)	48 (16)	34 (15)	14 (19)	0.56†
Clozapine, n (%)	13 (4)	11 (5)	2 (3)	0.53‡
Risperidone, n (%)	18 (6)	12 (5)	6 (8)	0.40‡
Other, n (%)	11 (4)	9 (4)	2 (3)	1.00‡
Benzodiazepines, n (%)	191 (65)	145 (66)	46 (62)	0.76†
Anticholinergics, n (%)	22 (8)	15 (7)	7 (10)	0.60†
Biperiden, n (%)	2 (1)	1 (0.5)	1 (1)	0.44‡
Promethazine, n (%)	17 (6)	12 (5)	5 (7)	0.77‡
Other, n (%)	3 (1)	2 (1)	1 (1)	1.00‡
Opioids, n (%)	12 (4)	10 (5)	2 (3)	0.74‡
Polypharmacy present during ECT course, n (%)	120 (41)	86 (39)	34 (46)	0.35†
Mood disorder severity scores (in HDRS equivalents)				
At baseline, median (IQR)	25.0 (20.0–29.0)	25.0 (20.0–29.0)	26.0 (19.5–28.0)	0.87#
After the ECT course, median (IQR)	11.5 (6.0–16.0)	11.0 (6.5–16.5)	12.0 (5.0–16.0)	0.38#
Average improvement, mean ± SD	12.2 ± 9.4	11.3 ± 8.9	14.3 ± 10.5	0.18*
Score ≥50% decrease compared with baseline, n (%)**	48 (53)	32 (50)	16 (59)	0.21†

Continued next page

TABLE 1. *(Continued)*

	Total Sample (n = 295)	Patients Without sPIC (n = 221)	Patients With sPIC (n = 74)	*P*
Score ≤7 after ECT course, n (%)**	38 (37)	26 (36)	12 (39)	0.43†
Cognitive functioning scores (in MMSE equivalents) at baseline, median (IQR)	29 (26–30)	29 (25–30)	29 (27–30)	0.12#
Treatment characteristics				
Anesthetic medication				
Use of etomidate, n (%)	293 (99)	220 (99)	73 (99)	0.44‡
Dose of etomidate, median (IQR), mg	20.0 (16.0–20.0)	20.0 (16.0–20.0)	20.0 (18.0–20.0)	**0.05**#
Muscle relaxant				
Use of succinylcholine, n (%)	184 (96)	144 (97)	40 (95)	1.00‡
Dose of succinylcholine, mg	75 (75–100)	75 (75–100)	100 (75–100)	**0.02**#
Use of flumazenil, n (%)	83 (28)	57 (26)	26 (35)	0.07†
Used pulse width during the course				
0.25 ms, n (%)	5 (2)	4 (2)	1 (1)	1.00‡
0.5 ms, n (%)	197 (67)	142 (64)	55 (74)	0.15†
0.75 ms, n (%)	7 (2)	6 (3)	1 (1)	0.68‡
1.0 ms, n (%)	86 (29)	69 (31)	17 (23)	0.23†
Dosage method used				
Dose-titration method, n (%)	149 (51)	111 (50)	38 (51)	0.69†
Half age method, n (%)	103 (35)	74 (34)	29 (39)	0.80†
Use of dose from past ECT, n (%)	24 (8)	17 (8)	7 (10)	0.98†
Position electrodes at start ECT				
Bifrontotemporal position, n (%)	169 (57)	126 (57)	43 (58)	0.98†
RUL position, n (%)	126 (43)	95 (43)	31 (42)	0.98†
Switch of electrode placement during the ECT course, n (%)	80 (26)	58 (26)	20 (27)	0.90†
Total amount of ECT sessions, median (IQR)	15.0 (10.0–21.0)	15.0 (11.0–21.0)	14.5 (10.0–20.3)	0.75#
ECT dose, mC	202 (151–277)	214 (148–265)	202 (151–302)	0.75#
EMG seizure duration, median (IQR), s	44.0 (33.7–58.6)	44.8 (34.3–58.3)	43.5 (32.0–60.0)	0.55#
EEG seizure duration, median (IQR), s	67.0 (49.3–85.8)	67.5 (51.1–85.7)	66.0 (45.0–86.5)	0.75#

Bold text indicates significance, $P \leq 0.05$. When applying a Bonferonni correction, a P value of ≤0.00074 is considered significant. None of the variables was significant after correction.

*Independent *t* test.

†χ^2 test.

‡Fisher exact test (2-sided).

§Maximum 1 year before start ECT.

||This includes all types of atrophy; no distinction was made between medial temporal lobe atrophy or general cortical atrophy.

¶Percentage is shown of available MRIs .

#Mann-Whitney *U* test.

**Percentage of available mood disorder severity scores.

MMSE indicates Mini-Mental State Examination; SNRI, selective serotonin and noradrenalin reuptake inhibitor; TCA, tricyclic antidepressant.

Characteristics of Patients With sPIC and Interventions

Patients who showed sPIC in at least 1 ECT session (n = 74) had a mean ± SD age of 57 ± 13 years, and 34 patients (47%) were male (Table 1). Most of these patients developed sPIC after the first ECT session (n = 26 [35%]; Fig. 1), in which, in half of the cases (n = 38 [51%]), a dose-titration procedure took place. All of the patients with sPIC received a pharmacological intervention to control the situation: 46 patients (62%) received benzodiazepines, 35 patients (47%) received propofol, and 3 patients (4%) received haloperidol (Table 2). To ensure the patients' (and sometimes also surroundings') safety, 7 patients (9%) needed physical restraints besides extra medication, and 4 patients (5%) had to be transferred to the closed ward or seclusion room. Clinical outcome of the ECT course in patients experiencing sPIC was generally satisfactory (median HDRS equivalents after the ECT course, 12.0; IQR, 5.0–16.0; average HDRS equivalents decrease, 12 points; response rate, 54%; remission rate, 31%) and did not significantly differ compared with patients without sPIC ($\chi^2_2 = 0.016$, $P = 0.89$ [response rate]; Fisher exact test, $P = 0.73$ [remission rate]; Mann-Whitney *U* test, 183; $Z = -1.50$; $P = 0.89$ [median decrease HDRS equivalents]). Only 2 patients (2.7%) showing sPIC discontinued their ECT course because of the occurrence of sPIC; in respect of the total sample (n = 295), discontinuation appeared in 0.7% of the ECT patients.

DISCUSSION

In this retrospective study of a naturalistic sample of 295 ECT patients, a quarter of the patients suffered sPIC in at least 1

TABLE 2. Characteristics of 74 Patients Who Showed sPIC After at Least 1 Session of ECT

	n (%)
Clinical and treatment characteristics	
Patient received previous ECT course(s)	14 (19)
Reoccurrence of sPIC after the initial occurrence	34 (46)
Termination of ECT course because of sPIC	2 (3)
Used interventions to control sPIC	
Pharmacological intervention	74 (100)
Benzodiazepines	46 (62)
Propofol	35 (47)
Haloperidol	3 (4)
Other	2 (1)
Usage of restraints	7 (9)
Transference to closed ward or seclusion room	4 (5)

ECT session, which urged for extra sedative medication and in 9% for physical restraints to ensure safety. However, the clinical outcome of ECT did not differ between patients who experienced sPIC and those who did not, and only 2 patients (0.7%) discontinued the ECT course because of sPIC. Patients who suffered sPIC, compared with those who did not, were more often male, less often showed catatonic features, more often reported history of CVA, did not use concomitant SSRIs, had been given higher doses of succinylcholine, and were more often pretreated with flumazenil. However, univariate results did not survive adjustments for multiplicity, and multivariate analyses with split-sample validation revealed no robust predictive model for the occurrence of sPIC. Therefore, the results should be interpreted with caution.

Prevalence of sPIC

The prevalence of 25% in this cohort compares with the prevalence found in the literature (ie, 16%–39.9%), although other studies included smaller sample sizes (ie, n = 203,[4] n = 96,[5] and n = 79[6]). Strikingly, only 0.7% of our patients discontinued ECT because of this severe adverse effect, although sPIC occurred repeatedly in 46% during the rest of the ECT course and physical restraints had to be used in 9%. Possibly, because sPIC is often short-lasting (ie, minutes to a few hours), proper treatment with sedatives is available, and occurrence of sPIC does not seem to affect the outcome of ECT (as we showed in our sample as well); these factors may have motivated the patient and psychiatrist to continue the ECT course. Nevertheless, occurrence of sPIC is a significant clinical problem, which has been given little attention in the current literature.

Diagnostic and Treatment Characteristics

In contrast to the systematic review of Tsujii et al,[7] our study revealed no associations between occurrence of sPIC and Parkinson disease, dementia, and BL electrode placement and even showed less occurrence of catatonic features and equal seizure durations between groups. Because independent training and test samples were used in our consecutive multivariate models, previously suggested individual diagnostic and treatment predictors of sPIC appear not likely to play an important role. Although none of the significant results of our univariate tests survived the Bonferroni corrections, some interesting trends were found which will now be discussed.

Sex Difference

In our sPIC group, more male patients were present than in the group without sPIC (46% vs 33%; $P = 0.05$). This finding has not been reported before, as other studies showed no difference between male and female patients.[7] It may be hypothesized that males show more often, or more severe, aggressive behavior during sPIC, which consequently may have caused more and quicker administration of interventions. However, in our sPIC group, the use of restraints was almost equally applied in females (n = 4) and in males (n = 3), possibly contradicting this hypothesis. Another explanation may be that other studies included less severe variants of postictal confusion as well.

History of CVA

In our sample, a higher prevalence of patients with a history of CVA appeared in the sPIC group (8% vs 2% in patients without sPIC; $P = 0.02$). On the other hand, the presence of cerebral ischemic damage on available MRI scans did not differ between both groups. Possibly, this may be explained by selection bias, because having had a recent CVA is a contraindication for ECT. In the literature, not much is reported about (history of) CVA related to sPIC in ECT.[7] One study in patients with a history of CVA (n = 28) showed no differences between patients with or without interictal delirium.[24] Also, it was hypothesized that damage in subcortical structures might be associated with postictal delirium in ECT.[25,26] Because our subsample of patients with a history of CVA was very small (n = 10), future prospective studies in much larger ECT populations may elucidate the influence of brain damage on the occurrence of sPIC.

Use of Concomitant Medication

Because earlier retrospective studies showed more occurrence of sPIC in concomitant users of quetiapine, lithium carbonate, and antidepressants[9,10] and less occurrence with olanzapine,[8] dexmedetomidine,[7,11] and anticholinergics medication,[7,12] we expected to find some associations in our sample as well. Interestingly, the only significant finding was that none of the ECT patients with sPIC used concomitant SSRIs ($P = 0.01$), maybe suggesting some preventive effect of SSRIs. Use of other antidepressants was registered equally in both groups. Although concomitant medication use appeared regular practice in our sample (eg, 41% even showed polypharmacy with more than 5 different medications), no differences were found between patients with or without sPIC, maybe because of a type II error. Moreover, medians of administered doses of quetiapine and olanzapine, as well as blood levels of lithium carbonate, did not differ between patients with or without sPIC (data not shown). Further research with larger sample sizes is needed to investigate the relationship between the use of antidepressants and the occurrence sPIC, especially SSRI usage.

Dosage of Succinylcholine

The used median dosage of succinylcholine was higher in patients showing sPIC compared with the no-sPIC group ($P = 0.02$). This finding is consistent with results from Reti et al,[5] although their results did not reach significance, possibly because of a smaller study population (n = 96). Possibly, our patients who had been administered higher dosage of succinylcholine experienced prolonged (some) muscle weakness and respiratory insufficiency in the postictal phase, which may have led to more sPIC. However, we did not find such observations in our charts. In daily clinical practice, this finding may stimulate anesthesiologists to use the lowest possible dosages of succinylcholine in ECT

patients. Further randomized clinical trials, though, are needed to examine this possible association.

Pretreatment With Flumazenil

The use of flumazenil appeared more frequent in patients who showed sPIC compared with no-sPIC ($P = 0.07$). Flumazenil has altering effects on the γ-aminobutyric acid receptors of the brain[27] and may, therefore, influence the patients' perception when waking up after ECT. Moreover, patients vulnerable for panic attacks may experience increase of anxiety after use of flumazenil,[28] which may play a role too in several ECT patients with comorbid panic disorder. Furthermore, flumazenil is known to induce agitation and anxiety in patients with benzodiazepine intoxication.[27] Therefore, our findings stimulate future prospective studies to examine the pros and cons of pretreatment with flumazenil in ECT.

Strengths and Limitations

This retrospective, naturalistic study has several strengths and weaknesses. Above all, by its retrospective nature, this study could not reveal any causal relationships between patient and treatment characteristics and the occurrence of sPIC. Also, it is important to note that our used definition of sPIC would have influenced the results. We scrutinized for the administration of extra medication and use of physically restraints and other serious interventions directly after the ECT session, as signs of the occurrence of clinically relevant sPIC. Because the recording of such interventions in the EMR is mandatory by law in the Netherlands, we think that our data set was quite reliable and complete. In the present literature, though, several definitions are being used for sPIC (eg, "postictal confusion," "postictal delirium," "postictal agitation"),[7,29] which hampers comparison with our results. The used definition of sPIC in our study is very similar to the definition of "agitated state" in the Richmond Agitation Sedation Scale (RASS),[30] as was used in other relevant studies.[4,5,8] However and unfortunately, in our retrospective study, such an objectifiable scale was not available because use of (for example) the RASS is time-consuming and, therefore, not a standard practice in our hospital. For future studies, it is therefore advised to use a reproducible definition for sPIC, such as the RASS.

Apparent univariate differences between the sPIC and no-sPIC groups did not survive Bonferroni correction for multiple comparisons in the univariate analyses. Also, some significant results appeared in very small subgroups (eg, history of CVA and concomitant use of SSRIs). However, trends were found in our univariate analysis. Therefore, we think that we may draw some conclusions and suggest further study regarding the clinical ECT practice (ie, use of concomitant SSRIs, dosage of succinylcholine, and pretreatment with flumazenil). Finally, we have used rigorous methods to assess independent predictors of sPIC, but none of our multivariate analyses revealed any robust predictive model. Also, local protocols to administer ECT (eg, which anesthetic is used for induction, whether regularly anticholinergic agent is used as premedication, which frequency of ECT sessions per week is chosen) may vary between treatment facilities, and this may hamper comparability with other samples. This shows the importance of the use of independent training and test data sets, before drawing robust conclusions about predictors and generalizing these to all treatments. Therefore, the field is still left with uncertainty about the patients' individual risks for sPIC, although outcome of ECT seems not affected by this nasty adverse effect.

In conclusion, this retrospective study, in a naturalistic sample of 295 ECT patients, showed a prevalence of sPIC, at least at 1 ECT session, of 25%. Severe postictal confusion made acute interventions necessary but resulted hardly in discontinuation of ECT, and treatment outcome was comparable with patients without experiencing sPIC. Patients showing sPIC, compared with those who did not, seemed to be characterized by male sex, a history of CVA, receiving higher dosage of succinylcholine, and pretreatment with flumazenil, as well as showing less catatonic features and no use of concomitant SSRIs. However, multivariate regression analyses using independent training and test sets revealed no independent predictors of sPIC, pointing at the importance of using independent training and test data sets. Therefore, the field is still left with uncertainty about the patients' individual risks for sPIC, but in daily clinical practice, the use of SSRIs, height of succinylcholine dose, and pretreatment with flumazenil may be evaluated, especially if patients suffer sPIC after ECT sessions.

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