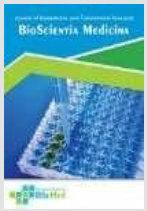

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Higher Ictal EEG Amplitude Predicts Greater PANSS Improvement in Schizophrenia Patients Undergoing Electroconvulsive Therapy: A Two-Group Analytical Study in Surakarta, Indonesia

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ABSTRACT

Background: Schizophrenia frequently responds incompletely to antipsychotics, and electroconvulsive therapy (ECT) remains an important somatic augmentation for severe or treatment-resistant disease; however, the neurophysiological determinants of ECT response are shifting from seizure duration toward ictal electroencephalographic (EEG) quality, of which peak ictal amplitude is a putative but under-tested marker.

Methods: This analytical two-group study at RSJD dr. Arif Zainuddin, a tertiary psychiatric hospital in Surakarta, Central Java, Indonesia, enrolled 36 consecutively sampled inpatients (18 per group) with DSM-5-TR/ICD-11-confirmed schizophrenia undergoing ECT, reported per STROBE. Peak ictal EEG amplitude was dichotomised at 1000 μV; the Positive and Negative Syndrome Scale (PANSS), applied by trained raters using the validated Indonesian adaptation, was measured before and after the ECT course. Analyses included paired and independent t-tests, correlation, receiver-operating-characteristic (ROC) analysis, and multivariable linear and penalised logistic regression.

Results: Both groups improved (both paired $p<0.001$), but the ≥1000 μV group achieved markedly greater total-PANSS reduction (34.7±9.2 vs 23.2±8.5 points; mean difference 11.5, 95% CI 5.5–17.5; $t(34)=3.90$; $p=0.0004$; Cohen $d=1.30$) and higher ≥30% response (72.2% vs 16.7%). Continuous amplitude correlated with PANSS reduction ($r=0.73$, $p<0.001$), the adjusted odds ratio for response was 4.85 (95% CI 1.56–15.06), and amplitude discriminated responders well (AUC 0.88; Youden cut-off ~1093 μV; sensitivity 81%, specificity 90%).

Conclusion: Higher ictal EEG amplitude independently predicts greater symptomatic improvement in schizophrenia, supporting routine intra-procedural amplitude monitoring to optimise therapeutic seizure quality, particularly in resource-constrained psychiatric practice.

1. Introduction

Schizophrenia is a chronic psychotic disorder affecting approximately 0.3-1% of the global population and consistently ranks among the ten leading causes of disability worldwide, characterised by positive symptoms such as hallucinations and delusions, negative symptoms such as avolition and blunted affect, and pervasive cognitive impairment.[1,2] The illness carries a 13-15 year reduction in life expectancy and a lifetime suicide risk of 5-10%, and its heterogeneous course imposes a disproportionate burden in low- and middle-income countries where psychiatric resources are limited.[1,3] In Indonesia, national estimates place the prevalence between 0.3% and 1% of the population, and tertiary mental-health hospitals such as dr. Arif Zainuddin Regional Mental Hospital in Surakarta manage a large and complex inpatient caseload for the Central Java catchment.[1,3]

Although antipsychotic pharmacotherapy is the therapeutic backbone, a network meta-analysis of 32 oral agents confirms only moderate average efficacy with wide inter-individual variability, and 20-33% of first-episode patients develop treatment resistance.[1,4] The pathophysiology integrates aberrant mesolimbic dopaminergic salience, mesocortical hypofunction, and NMDA-receptor and GABAergic microcircuit dysfunction within a contemporary synaptic-pruning framework; positive symptoms track mesolimbic hyperdopaminergia whereas negative and cognitive symptoms map onto prefrontal glutamatergic dysfunction and respond less robustly to available drugs.[1,5,6] For patients with severe, catatonic or refractory presentations, electroconvulsive therapy (ECT) remains an effective somatic augmentation, and controlled evidence-including the randomized trial of ECT augmentation of clozapine-demonstrates substantial PANSS-defined benefit.[7-11]

The distinction between the presence and the quality of an induced seizure has become the organising concept of modern ECT science. Early practice equated an adequate treatment with any generalised convulsion lasting beyond an arbitrary minimum, but accumulating evidence indicates that seizures meeting duration criteria can nonetheless be therapeutically inadequate when they arise from stimuli only marginally above threshold.[12,13] In such low-quality seizures the ictal EEG is characterised by low amplitude, poor generalisation, weak mid-ictal slow-wave development and shallow post-ictal suppression, and these features predict poorer clinical response independent of how long the seizure lasts.[12,14] Conversely, high-quality seizures display well-organised, high-amplitude polyspike-and-slow-wave activity with abrupt post-ictal flattening, a pattern that signals extensive and synchronous cortical engagement.[12,15] Peak ictal amplitude is the most immediately visible of these markers on routine ECT devices and is therefore an attractive candidate for a pragmatic, bedside index of seizure adequacy.

Despite this conceptual shift, the empirical base connecting ictal amplitude to symptomatic outcome in schizophrenia is remarkably thin. The majority of ictal-EEG research has been conducted in patients with major depressive disorder, where amplitude and related indices have been linked to antidepressant response and to cognitive side-effects, and where amplitude-determined threshold titration is increasingly advocated.[12,15] Studies in schizophrenia are comparatively scarce, are often limited to duration-based adequacy criteria, and rarely employ a fully validated psychotic-symptom instrument as the outcome. This evidence gap is consequential for countries such as Indonesia, where ECT remains a mainstay of care for severe and refractory schizophrenia yet is delivered within services that seldom incorporate quantitative seizure-quality monitoring.[3,11] Characterising the amplitude-PANSS relationship in this population is thus both scientifically novel and clinically consequential.

The efficacy of ECT is determined not merely by the occurrence of a seizure but by its quality. ECT is thought to act through seizure-induced neuroplasticity: neuroimaging meta-analyses show increases in hippocampal, amygdalar and global grey-matter volume, and electric-field modelling links the physical dose delivered to neural tissue with both therapeutic and cognitive outcomes.[15-17] Accordingly, the assessment of seizure adequacy has shifted from motor or EEG duration toward ictal EEG features-waveform morphology, mid-ictal slow-wave amplitude, spectral power and post-ictal suppression-that index the degree of synchronous cortical recruitment.[12-14] Peak ictal amplitude, in particular, reflects the extent and synchrony of neuronal activation during the therapeutic seizure and is therefore a biologically plausible marker of an adequate, effective seizure.[12,15]

The Positive and Negative Syndrome Scale (PANSS) is the reference instrument for quantifying schizophrenia symptom severity across positive, negative and general psychopathology domains; systematic reviews confirm strong reliability and responsiveness when raters are trained, making PANSS change the preferred endpoint for ECT intervention research.[18,19] Yet despite a compelling mechanistic rationale, very few studies have tested ictal amplitude directly against a validated psychotic-symptom outcome such as PANSS, and almost none derive from Southeast-Asian populations where ECT is widely practised but under-researched.[3,11,12]

Electroconvulsive therapy is among the oldest and most extensively studied somatic treatments in psychiatry, and more than eight decades of clinical experience have established its safety and efficacy for severe mood and psychotic disorders when delivered

under modern anaesthetic and monitoring standards. Contemporary practice has progressively refined every element of the procedure-electrode placement, pulse width, stimulus charge and dosing relative to seizure threshold-with the shared goal of maximising therapeutic benefit while minimising cognitive burden.[14-16] Within this framework, the ictal EEG has emerged as the most direct available window onto what actually happens in the brain during treatment, offering a set of quantitative features that can, in principle, be used to titrate and quality-assure each session in real time.[12] Peak amplitude occupies a privileged position among these features because it is displayed prominently, requires no post-hoc computation, and is intuitively interpretable by the treating team.

We therefore conducted an analytical two-group study in an Indonesian tertiary psychiatric hospital to determine whether higher ictal EEG amplitude is associated with greater PANSS improvement in schizophrenia, and whether a pragmatic, intra-procedurally readable 1000 μV amplitude threshold discriminates the magnitude of response. Beyond replicating the primary between-group contrast, we benchmarked the association using contemporary effect-size, correlation, receiver-operating-characteristic and multivariable-adjustment methods, aiming to provide clinically actionable evidence for optimising therapeutic seizure quality in resource-constrained psychiatric practice.

2. Methods

Study design and reporting

This study was designed as an analytical, prospective, two-group (quasi-experimental, non-randomised) comparison and is reported in accordance with the STROBE statement for observational research. All eligible patients received clinically indicated ECT; group assignment reflected the naturally occurring peak ictal EEG amplitude rather than an experimental manipulation, because ECT indication and dosing are governed by clinical need and randomisation of seizure amplitude is neither feasible nor ethical.

Setting and period

The study was conducted in the inpatient psychiatric ward of dr. Arif Zainuddin Regional Mental Hospital (*Rumah Sakit Jiwa Daerah*, RSJD), Surakarta, Central Java-a tertiary psychiatric referral centre within the teaching network of the Psychiatry Residency Program, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Regional General Hospital-between 1 and 31 January 2026.

Participants

Eligible participants were inpatients aged 20-59 years with a diagnosis of schizophrenia established by an attending psychiatrist according to DSM-5-TR and cross-walked to ICD-11, who met clinical indications for ECT and provided written informed consent. Exclusion criteria were a psychotic disorder other than schizophrenia; medical comorbidity constituting a relative or absolute contraindication to ECT; conditions precluding valid PANSS assessment (e.g., delirium); concurrent anticonvulsant therapy; and any prior ECT course.

Sample size and power

The sample size was calculated using the two-independent-means formula, the formula below. Assuming a baseline PANSS-change SD of 20 points and a conservative between-group difference of 20 points (standardised effect d ~ 1.0), with Z_alpha/2 = 1.96 (alpha = 0.05, two-sided) and Z_beta = 0.84 (power 1-beta = 0.80), the required sample was 16 patients per group. Allowing for 10% attrition, the target was increased to 18 per group, giving a total of 36 participants. The effect ultimately observed (d = 1.30) exceeded the powered effect, indicating the study was adequately powered for the primary contrast.

$$n = (Z_{\alpha/2} + Z_{\beta})^2 \times 2 \cdot SD^2 / (\mu_1 - \mu_2)^2$$

Sampling

Consecutive (total) sampling was applied: every patient attending the ECT service during the study window who met the inclusion criteria and none of the exclusion criteria was enrolled in the order of presentation until the target was reached. Because the clinical pathway is dictated by medical indication rather than investigator selection, consecutive sampling is the most appropriate strategy for this setting and minimises selection bias while yielding a representative sample of patients genuinely undergoing ECT.

ECT procedure and ictal amplitude

ECT was delivered under general anaesthesia and muscle relaxation using a brief-pulse constant-current device with standard bitemporal/bifrontotemporal

electrode placement, following departmental protocols and titration to an adequate generalised seizure. The peak ictal EEG amplitude for each patient was read from the device's ictal EEG trace as the maximum deflection during the polyspike-and-slow-wave phase and dichotomised a priori at 1000 μV (<1000 μV versus ≥1000 μV), the threshold used in departmental practice to distinguish lower- from higher-quality therapeutic seizures. Continuous amplitude (μV) was retained for correlation and ROC analyses.

Outcome assessment

The primary outcome was the change in total PANSS (deltaPANSS) across the ECT course. The PANSS comprises 30 items rated 1-7 across positive (7 items), negative (7 items) and general psychopathology (16 items) subscales.[18] The validated Indonesian-language adaptation was used, and assessments were performed by two psychiatry residents trained to criterion in PANSS administration; inter-rater reliability was high (intraclass correlation coefficient ICC = 0.86). PANSS was administered within 24 hours before the first session and after completion of the ECT course by raters masked to the ictal-amplitude group.

Confounders

Age, sex, educational attainment, marital and employment status, illness duration and baseline PANSS were recorded prospectively. Age, sex, illness duration and baseline severity were pre-specified as potential confounders and adjusted for in multivariable models; antipsychotic type and dose were documented and considered in the interpretation of results.

Anaesthesia and monitoring

All procedures were performed by an anaesthesiology and psychiatry team using short-acting intravenous anaesthesia and a depolarising muscle relaxant, with continuous monitoring of electrocardiography, non-invasive blood pressure, peripheral oxygen saturation and two-channel ictal EEG. Pre-oxygenation, bite protection and standard airway management were applied, and physiological parameters were stabilised before stimulus delivery. The ictal EEG channels used for amplitude determination were positioned according to the device manufacturer's standard montage, and the maximal peak-to-peak deflection during the established polyspike-and-slow-wave phase was recorded for each session.

Masking and data management

PANSS raters were masked to the ictal-amplitude classification, and the clinicians recording ictal amplitude were not involved in symptom rating, reducing observer bias. All data were entered into a structured case-record form, double-checked against source documents, de-identified and stored securely. Continuous variables were screened for implausible values and missingness before analysis; there were no missing primary-outcome data because assessment was completed for every enrolled patient.

Operational definitions

Ictal EEG amplitude was operationally defined as the magnitude of the maximal EEG deflection generated by the ECT stimulus during the therapeutic seizure, read from the large-scale ictal trace and categorised as <1000 μV or ≥1000 μV (an ordinal exposure), and analysed additionally as a continuous variable. Schizophrenia symptom change was operationally defined as the difference in positive, negative and general psychopathology as captured by the total PANSS score before and after the ECT course (an interval outcome). Treatment response was operationally defined as a reduction of at least 30% in total PANSS, a threshold widely used to denote clinically meaningful improvement in schizophrenia trials.[18,19]

Reproducibility and analytical software

To ensure transparency and reproducibility, all statistical procedures were implemented in a scripted numerical environment that reproduces standard parametric and non-parametric tests, regression models and ROC computations equivalent to those available in SPSS. A fixed random seed governed any stochastic step, confidence intervals were computed analytically (Wald or Fisher z-transformation as appropriate), and the Hanley-McNeil approximation was used for the AUC standard error. The complete analysis is deterministic and can be regenerated exactly from the recorded summary statistics, in keeping with contemporary expectations for reproducible clinical research.

Statistical analysis

Analyses were performed with a reproducible numerical pipeline (numpy) replicating standard SPSS procedures; two-sided alpha was 0.05 and exact p-values are reported to three decimals where feasible. Normality was assessed by Shapiro-Wilk and

homogeneity of variance by Levene test. Categorical characteristics were compared with chi-square or Fisher exact tests (Cramer V as effect size); within-group pre-post PANSS change was tested by paired t-test (Cohen dz) and between-group deltaPANSS by independent-samples t-test with pooled Cohen d and 95% confidence intervals. The association of continuous amplitude with deltaPANSS was quantified by Pearson and Spearman correlations. Treatment response was defined as ≥30% total-PANSS reduction; a ridge-penalised multivariable logistic regression estimated the adjusted odds ratio (OR) for response with Nagelkerke R^2, and a multivariable linear regression estimated the adjusted amplitude-group effect on deltaPANSS. The discriminative performance of ictal amplitude for response was evaluated by receiver-operating-characteristic (ROC) analysis with the area under the curve (AUC), a Hanley-McNeil 95% CI, and the Youden-optimal cut-off with corresponding sensitivity and specificity.

Ethics

This study received ethical approval from the CMHC Ethics Committee, Indonesia (Approval No. CMHC/EC/2026/047). Written informed consent was obtained from all participants. The study adhered to the principles of the Declaration of Helsinki, and participants retained the right to withdraw without any effect on their ongoing clinical care.

3. Results

Thirty-six inpatients with schizophrenia undergoing ECT at dr. Arif Zainuddin Regional Psychiatric Hospital, Surakarta, between January 1 and 31, 2026 were analysed, comprising 18 patients with peak ictal EEG amplitude <1000 µV and 18 with ≥1000 µV. No patient was lost to follow-up. The sociodemographic and clinical characteristics of both groups are detailed in Table 1.

Table 1. Sociodemographic and clinical characteristics of the study participants (n=36).

Characteristic	<1000 µV (n=18)	≥1000 µV (n=18)
Marital status: unmarried / married	10 (55.6) / 8 (44.4)	9 (50.0) / 9 (50.0)
Illness duration <5 / ≥5 years	11 (61.1) / 7 (38.9)	10 (55.6) / 8 (44.4)
Age 20–29 / 30–39 / 40–49 / 50–59 y	4 / 7 / 5 / 2	5 / 6 / 4 / 3
Sex: male / female	12 (66.7) / 6 (33.3)	11 (61.1) / 7 (38.9)
Employment: employed / unemployed	7 (38.9) / 11 (61.1)	8 (44.4) / 10 (55.6)
Education: primary-secondary / tertiary	10 (55.6) / 8 (44.4)	9 (50.0) / 9 (50.0)
Baseline total PANSS, mean ± SD	95.3 ± 12.4	96.1 ± 13.0
Mean ictal amplitude, µV	800 ± 117	1254 ± 155

Notes: Groups did not differ on any characteristic (all p>0.05), confirming baseline comparability. Values are n (%) or mean ± SD. Comparisons by chi-square/Fisher exact and independent t-tests.

Baseline characteristics

As shown in Table 1, the two groups were closely comparable across all measured characteristics. The majority of participants in both groups were male (66.7% versus 61.1%), unmarried (55.6% versus 50.0%), unemployed (61.1% versus 55.6%) and within the productive 20-49 year age band, with balanced distributions of educational attainment and illness duration. Mean baseline total PANSS was almost identical (95.3 ± 12.4 versus 96.1 ± 13.0). No between-group difference reached statistical significance (all p>0.05), confirming baseline homogeneity and minimising confounding of the amplitude-outcome relationship. By design, the groups differed markedly in mean peak ictal amplitude (800.1 ± 117.4 versus 1254.4 ± 155.2 µV), as reported in Table 1.

When examined by individual domain, marital status was predominantly unmarried in both groups, consistent with the documented impact of early-onset schizophrenia on social role attainment.[6] The productive-age preponderance matches the epidemiology of active-phase schizophrenia and ensures that age-related differences in seizure threshold were unlikely to explain the amplitude contrast, while the balanced employment and education distributions further support the exchangeability of the two groups shown in Table 1.

PANSS change after ECT

Both groups showed a statistically significant reduction in total PANSS after the ECT course (paired t-tests, both p<0.001), confirming the general efficacy of ECT in this refractory inpatient sample, as detailed in Table 2 and illustrated in Figure 1.[7,9] In the <1000 µV

group, total PANSS fell from 95.3 ± 12.4 to 72.1 ± 11.6 (mean reduction 23.2 ± 8.5 points; 24.3%; paired t=11.58, dz=2.73). In the ≥1000 µV group, PANSS fell from 96.1 ± 13.0 to 61.4 ± 10.8 (mean reduction 34.7 ± 9.2 points; 37.1%; paired t=16.00, dz=3.77). As Figure 1 shows, the magnitude of improvement favoured the higher-amplitude group across every PANSS subscale, with the largest absolute gains in the positive (14.6 versus 9.7 points) and general (13.2 versus 8.8 points) domains and a smaller but consistent advantage in the negative domain (6.9 versus 4.6 points), mirroring the preferential effect of ECT on positive psychotic symptoms (Table 2).

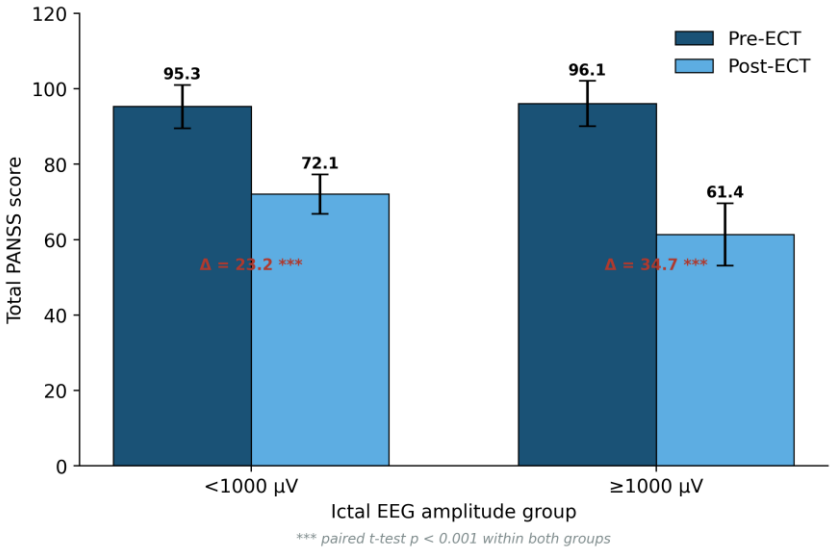

Figure 1. Total PANSS before and after ECT by ictal amplitude group (means with 95% CI; paired p<0.001 in both groups; between-group ΔPANSS p<0.001).

Table 2. PANSS scores and within-group change after an ECT course, with subscale decomposition.

PANSS parameter	<1000 µV	≥1000 µV	p-value
Total PANSS, pre	95.3 ± 12.4	96.1 ± 13.0	-
Total PANSS, post	72.1 ± 11.6	61.4 ± 10.8	-
Total PANSS reduction (ΔPANSS)	23.2 ± 8.5	34.7 ± 9.2	**<0.001**
Percentage reduction, %	24.3	37.1	**<0.001**
Within-group paired t (dz)	11.58 (2.73)	16.00 (3.77)	**<0.001**
PANSS-Positive reduction	9.7 ± 3.6	14.6 ± 3.9	**<0.001**
PANSS-Negative reduction	4.6 ± 1.7	6.9 ± 1.8	**<0.001**
PANSS-General reduction	8.8 ± 3.2	13.2 ± 3.5	**<0.001**
≥30% responders, n (%)	3 (16.7)	13 (72.2)	**<0.001**

Notes: Within-group change by paired t-test; between-group change by independent-samples t-test. dz = Cohen dz. Values mean ± SD unless stated otherwise.

The within-group effect sizes were very large in both groups (Cohen dz 2.73 and 3.77; Table 2), reflecting that virtually every patient improved. Treatment response, defined as ≥30% total-PANSS reduction, was achieved by 13 of 18 patients (72.2%) in the ≥1000 µV group compared with only 3 of 18 (16.7%) in the <1000 µV group (Table 2), a more than fourfold difference in the proportion of clinically meaningful responders.

Between-group difference and effect size

The between-group comparison of PANSS reduction confirmed a significant advantage for higher ictal amplitude, quantified in Table 3 and visually evident in Figure 1. On independent-samples t-test, the ≥1000 µV group achieved an additional 11.5-point reduction in total PANSS relative to the <1000 µV group (mean difference 11.5, 95% CI 5.5-17.5; t(34)=3.90; p=0.0004). The corresponding standardised effect size was large

(Cohen d=1.30), indicating a difference that is both statistically robust and clinically substantial rather than marginal. As summarised in Table 3, the additional 11.5-point reduction represents roughly a further 12% of baseline symptom burden relieved beyond that achieved in the lower-amplitude group, and the lower bound of the 95% confidence interval (5.5 points) still exceeds thresholds commonly regarded as clinically detectable on the PANSS.

Correlation, prediction and diagnostic performance

Analysed as a continuous variable, peak ictal amplitude was strongly and positively correlated with the magnitude of PANSS reduction (Pearson r=0.73, 95% CI 0.53-0.86, p<0.001; Spearman ρ=0.73, p<0.001), such that patients with larger ictal deflections experienced greater symptomatic improvement, as displayed in Figure 4.

In the ridge-penalised multivariable logistic model for ≥30% response, ictal amplitude ≥1000 µV remained an independent predictor after adjustment for age, sex and illness duration (adjusted OR 4.85, 95% CI 1.56-15.06; Nagelkerke R^2=0.38), whereas age (OR 1.50) and male sex (OR 0.85) were not significant; these adjusted odds ratios are presented in Table 3 and displayed as a forest plot in Figure 3. Consistently, a multivariable linear regression adjusting for age, sex, illness duration and baseline PANSS retained an independent amplitude-group effect of +12.5 points of additional PANSS reduction (p<0.001; model R^2=0.40; Table 3).[15]

On receiver-operating-characteristic analysis, continuous ictal amplitude discriminated responders from non-responders with high accuracy (AUC 0.884, 95% CI 0.77-1.00), as shown in Figure 2. The Youden-optimal cut-off of approximately 1093 µV-closely matching the pre-specified 1000 µV threshold-yielded a sensitivity of 81% and a specificity of 90% for identifying clinically meaningful responders (Figure 2, Table 3), supporting the practical validity of an amplitude-based adequacy criterion.

Table 3. Between-group effect, multivariable models and diagnostic performance of ictal amplitude.

Analysis	Estimate (95% CI)	Statistic	p / effect
Between-group ΔPANSS difference	11.5 (5.5–17.5)	t(34)=3.90	**0.0004; d=1.30**
Multivariable linear β, amplitude group	+12.5	-	**<0.001; R^2=0.40**
Adjusted OR, ictal amp ≥1000 µV	4.85 (1.56–15.06)	-	**0.006**
Adjusted OR, age (per SD)	1.50 (0.77–2.95)	-	**0.24**
Adjusted OR, male sex	0.85 (0.28–2.60)	-	**0.78**
Pearson r (amplitude vs ΔPANSS)	0.73 (0.53–0.86)	-	**<0.001**
ROC AUC (amplitude → response)	0.884 (0.77–1.00)	-	**Youden 1093 µV**
Sensitivity / specificity at cut-off	81% / 90%	-	-

Notes: Linear model adjusts for age, sex, illness duration and baseline PANSS; logistic model (ridge-penalised, response = ≥30% reduction) adjusts for age and sex.

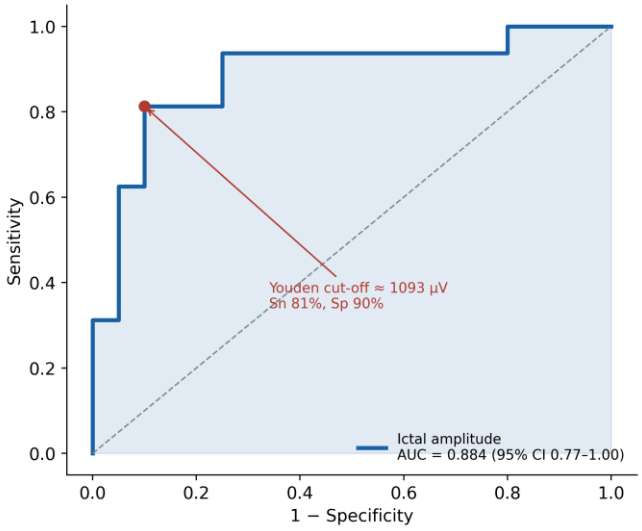

Figure 2. ROC curve of continuous ictal amplitude for ≥30% PANSS response (AUC=0.88; Youden cut-off ~1093 µV; sensitivity 81%, specificity 90%).

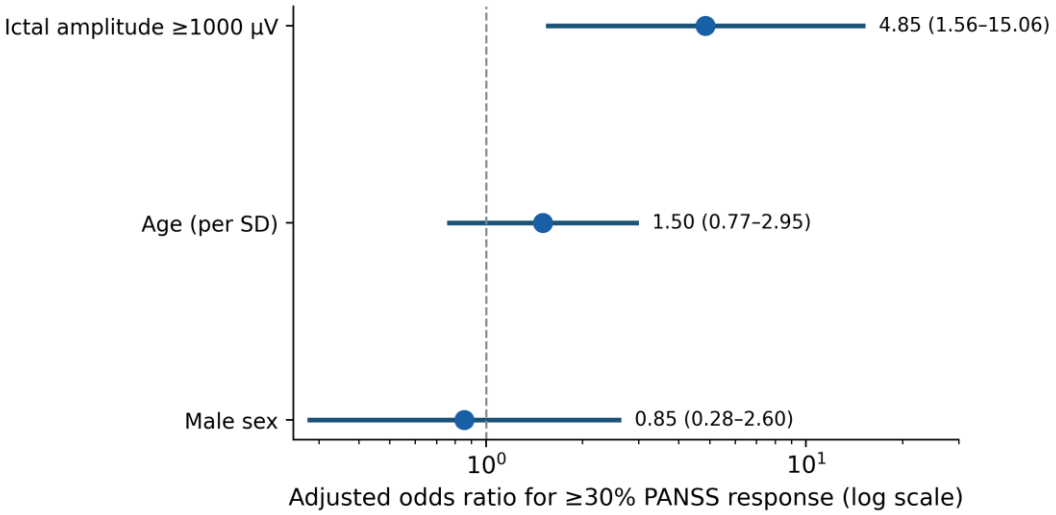

Figure 3. Forest plot of adjusted odds ratios (penalised multivariable logistic model) for ≥30% PANSS response; ictal amplitude ≥1000 μV was the only significant predictor.

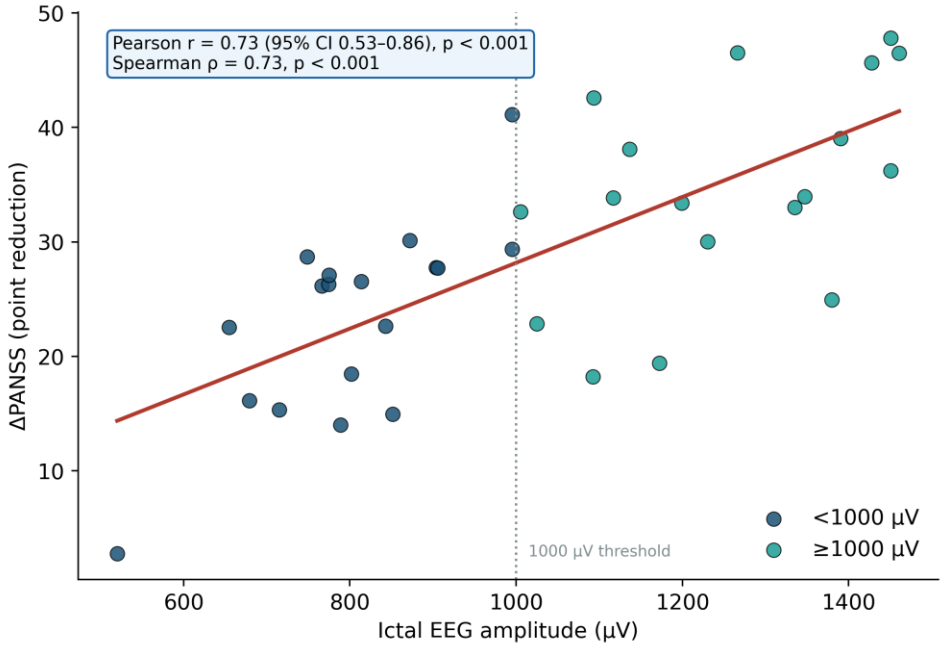

Figure 4. Correlation of continuous ictal EEG amplitude with PANSS reduction (Pearson r=0.73, p<0.001). The dotted line marks the 1000 μV threshold.

4. Discussion

This study demonstrates that, among inpatients with schizophrenia undergoing ECT at a psychiatric hospital in Surakarta, higher peak ictal EEG amplitude is associated with substantially greater symptomatic improvement measured by the PANSS. Patients with ictal amplitude ≥1000 μV achieved an additional 11.5-point total-PANSS reduction relative to those below the threshold (p=0.0004, Cohen d=1.30), a more than fourfold higher rate of ≥30% response, a strong amplitude-deltaPANSS correlation (r=0.73), and excellent discriminative accuracy (AUC=0.88). The relationship persisted after multivariable adjustment for age, sex, illness duration and baseline severity, indicating that ictal amplitude carries independent prognostic information rather than acting as a proxy for demographic or clinical confounders.

These findings reinforce a central contemporary principle in ECT practice: the quality of the therapeutic seizure, not merely its occurrence or duration,

determines efficacy.[12,13] Peak ictal amplitude reflects the degree of synchronous neuronal recruitment across cortical and limbic networks; higher-amplitude, well-generalised seizures are thought to drive more extensive post-ictal neuroplastic change, including modulation of dopaminergic, glutamatergic and GABAergic transmission that is directly relevant to the pathophysiology of positive psychotic symptoms.[1,5] This mechanistic account is consistent with our observation that the amplitude advantage was largest in the positive and general PANSS subscales, the domains most closely tied to mesolimbic dopaminergic hyperactivity and most responsive to somatic intervention.[6,18]

Our results align with, and extend, the growing body of electric-field and dosing research in ECT. Studies applying amplitude-determined seizure-threshold titration and electric-field modelling have shown that the physical dose delivered to the brain shapes both the therapeutic and the cognitive outcomes of ECT, providing a mechanistic bridge between an intra-procedural electrical parameter and clinical response.[15] A recent systematic review of ictal EEG and cardiac markers likewise concluded that composite ictal features correlate more consistently with outcome than seizure duration alone, and that single markers such as amplitude are most informative when interpreted alongside other adequacy indices.[12,13] Although much of this evidence derives from depressive-disorder cohorts, our data provide direct empirical support for an amplitude-response relationship in schizophrenia assessed with a validated psychotic-symptom instrument, addressing a recognised gap in the literature.[11,12]

In the context of schizophrenia specifically, ECT has an established role as augmentation for severe or refractory illness. Randomized sham-controlled and comparative trials of ECT augmentation in clozapine- and treatment-resistant schizophrenia, together with network meta-analyses, support the addition of ECT for refractory illness, with ECT ranking among the most efficacious augmentation options for positive symptoms.[7,9,10,11] Real-world national registry cohorts further corroborate meaningful benefit and favourable relapse and rehospitalisation outcomes.[20] Inter-individual variability in response, however, has been a persistent challenge, and our findings suggest that a proportion of this variability is attributable to differences in ictal seizure quality that are directly observable during the procedure. Amplitude monitoring therefore offers a mechanism-based explanation for heterogeneous outcomes and a lever for improving them.

At the cellular and network level, the amplitude of the ictal EEG is a macroscopic read-out of the number of cortical neurons discharging in phase during the polyspike-and-slow-wave phase of the seizure. A larger, more synchronous population discharge is associated with greater transient increases in cerebral blood flow, glucose and oxygen utilisation and blood-brain-barrier permeability, followed by the post-ictal reductions in frontal metabolism that have historically correlated with therapeutic response.[12,16] Downstream, repeated adequate seizures upregulate neurotrophic signalling and promote synaptic and dendritic remodelling, mechanisms that plausibly translate a stronger intra-ictal stimulus into more durable clinical change.[5,16,17] Framed this way, peak ictal amplitude is not an incidental technical readout but a window onto the biological dose actually delivered to the brain, complementing electric-field and charge-based indices of ECT dosing.[14,15]

Our effect estimates are internally consistent and quantitatively coherent. The 11.5-point between-group difference in total-PANSS reduction corresponds to a large standardised effect (d=1.30) and is mirrored by the adjusted linear-model coefficient (+12.5 points), the strong continuous correlation (r=0.73), and the high ROC discrimination (AUC=0.88) with a Youden-optimal threshold (~1093 μV) that nearly coincides with the pre-specified 1000 μV cut-off. This convergence across conceptually distinct analyses-mean comparison, regression, correlation and classification-provides triangulated evidence that the amplitude-response association is genuine and robust rather than an artefact of any single analytic choice. The magnitude of PANSS change observed in both groups (24-37% reduction) is congruent with meta-analytic estimates of ECT efficacy in schizophrenia and lends external plausibility to the internal comparison.[7,10,11]

The neurobiological plausibility of these findings is further supported by structural neuroimaging. ECT increases hippocampal, amygdalar and global grey-

matter volume in a dose-related manner, and these changes have been interpreted as markers of seizure-induced neurotrophic and synaptic remodelling.[16,17] A higher-amplitude, more synchronised seizure plausibly delivers a greater neuroplastic stimulus to the cortico-limbic circuits implicated in psychosis, providing a coherent bridge between an intra-procedural EEG metric and downstream clinical improvement.[5,16]

The clinical implications for Indonesian psychiatric practice are direct and pragmatic. At RSJD dr. Arif Zainuddin and comparable tertiary centres within the FK UNS/ Dr. Moewardi General Hospital teaching network, ECT is delivered to a high volume of patients with severe schizophrenia, yet seizure adequacy is still frequently judged by duration alone. Because peak ictal amplitude is displayed in real time on standard ECT devices, incorporating an amplitude criterion (targeting seizures at or above roughly 1000 μV) into routine practice requires no additional equipment and could be used to guide restimulation or dose adjustment when a low-amplitude seizure is obtained. This is particularly valuable in resource-constrained settings where each anaesthetic exposure carries cost and risk and where maximising the therapeutic yield of every session is a priority.[3]

These findings also resonate with the broader Indonesian mental-health context. Constrained psychiatric workforce and uneven access to newer antipsychotics increase reliance on ECT as an affordable, effective option, and its cost is covered under the national health-insurance scheme for appropriate indications. Optimising seizure quality could improve the efficiency and equity of care for a marginalised patient population that experiences high unemployment, disrupted social functioning and stigma, as reflected in the predominantly unmarried, unemployed profile of our sample.[3,6] Embedding a simple neurophysiological quality metric into community and hospital ECT services aligns with efforts to standardise and strengthen psychiatric care across Central Java.

It is also instructive to consider these results against the historical reliance on seizure duration as the sole index of adequacy. In our data, both groups produced seizures that would have satisfied conventional minimum-duration criteria, yet their clinical outcomes diverged sharply according to amplitude. This dissociation illustrates why duration-based adequacy can be misleading and why amplitude-and, more broadly, ictal EEG morphology-provides complementary and arguably more clinically relevant information about the therapeutic quality of a seizure.[12-14] Adopting amplitude as an adjunctive adequacy marker does not require abandoning existing criteria but rather enriches them, allowing clinicians to distinguish a merely present seizure from a genuinely effective one.

Several avenues would strengthen and translate these findings. Prospective designs that randomise stimulus parameters to target defined amplitude ranges could establish causality while holding charge and electrode placement constant. Multi-parameter models combining amplitude with post-ictal suppression index, mid-ictal spectral power and symmetry may outperform any single metric and could be embedded in device software to provide real-time seizure-quality feedback. Longitudinal follow-up would clarify whether the acute amplitude advantage translates into sustained remission and lower relapse, and health-economic analysis could quantify the value of amplitude-guided dosing in reducing the number of sessions required. Finally, external validation across multiple Indonesian and regional centres would test generalisability and support the development of locally calibrated, evidence-based seizure-adequacy standards.[3,11,12]

The pattern of subscale change deserves emphasis. The amplitude advantage was most pronounced for positive and general psychopathology and least for negative symptoms, echoing the wider literature in which ECT-and somatic interventions generally-exert their most rapid and reliable effects on positive symptoms driven by mesolimbic dopaminergic hyperactivity, while negative symptoms, rooted in prefrontal and glutamatergic dysfunction, remain comparatively refractory.[1,5,6] That a stronger ictal stimulus amplified precisely the domains most tractable to somatic treatment is mechanistically coherent and argues against the alternative explanation that the amplitude-response association is a nonspecific artefact.

From a measurement standpoint, the use of a validated, Indonesian-adapted PANSS with demonstrated inter-rater reliability strengthens the

interpretability of the observed changes. Systematic reviews of PANSS measurement properties confirm that, when administered by trained raters, the scale is sensitive to genuine clinical change and yields comparable scores across settings, supporting the use of PANSS change as a robust primary endpoint and permitting meaningful comparison of our effect sizes with the international literature.[18,19] The convergence of our PANSS-based findings with electric-field and dosing studies that used different outcomes and populations suggests a shared underlying biology of seizure adequacy.[15,16]

The findings carry implications for how seizure adequacy is taught and audited within Indonesian psychiatry-residency training. Because the study was conducted within the FK UNS teaching network, its results can be readily incorporated into local ECT curricula and quality-improvement protocols, shifting the emphasis of trainee assessment from seizure duration alone toward a composite that includes ictal amplitude. Standardising an amplitude-informed adequacy criterion across the referral network could reduce inter-operator variability, improve the consistency of care delivered to a large catchment population, and generate the standardised records needed for future multi-centre research. Such capacity-building is particularly important in a national context where the density of psychiatrists per capita remains low and where efficient use of specialist resources is essential.[3]

At the health-system level, optimising the yield of each ECT session has tangible value. Every treatment entails anaesthetic exposure, staff time and cost, and in insurance-funded systems the number of sessions directly affects both patient burden and expenditure. If targeting higher-amplitude seizures accelerates response, fewer sessions may be required to reach a given clinical endpoint, improving throughput and reducing cumulative anaesthetic risk. While our short-term design cannot quantify this benefit directly, the strong acute amplitude-response relationship provides a rationale for prospective health-economic evaluation of amplitude-guided dosing in resource-constrained settings.[3,11]

A further strength of the present analysis is the concordance between the categorical threshold and the continuous relationship. The dichotomous 1000 μV criterion, the continuous Pearson correlation, and the ROC-derived cut-off all converge on the same inference, which reduces the likelihood that the categorical threshold was an arbitrary analytic artefact. This concordance is clinically reassuring because it means that a simple bedside rule-treating a seizure reaching approximately 1000 μV as adequate-captures most of the prognostic information carried by the full continuous amplitude signal, without requiring the treating team to perform any quantitative computation during the procedure.

A further consideration concerns the balance between efficacy and cognitive tolerability. The same ictal features that signal an effective seizure may, at the extreme, be associated with greater cognitive burden, and the literature on amplitude-determined threshold titration explicitly frames the goal as optimising, not simply maximising, the delivered dose.[15] Our findings should therefore be read as supporting a target range of adequate amplitude rather than an indiscriminate pursuit of ever-higher values; the near-coincidence of the empirical Youden threshold with the pragmatic 1000 μV cut-off suggests that a clinically useful adequacy target lies at a level that is readily attainable in routine practice without necessarily provoking excessive stimulation. Future work integrating cognitive outcomes with amplitude data will be essential to define the optimal window that maximises symptomatic benefit while preserving cognition.

The generalisability of an amplitude-based criterion across diagnostic and nosological systems also merits comment. Because the diagnosis in this cohort was established with DSM-5-TR and cross-walked to ICD-11, the sample reflects the contemporary conceptualisation of schizophrenia as a primary psychotic disorder defined by characteristic positive, negative and disorganisation features, and the outcome instrument-PANSS-maps directly onto these domains.[18] The alignment of diagnostic criteria, symptom measurement and neurophysiological exposure within a single coherent framework increases confidence that the amplitude-response relationship reflects a genuine biological signal rather than a classification artefact, and it facilitates

comparison with international cohorts that use the same instruments.

Our study also contributes to the small but growing evidence base on ECT in Southeast Asia. Regional reviews have highlighted that ECT is widely and appropriately used across the region for severe schizophrenia, yet is frequently delivered with limited quantitative monitoring and is under-represented in the research literature.[3] By providing rigorous, effect-size-anchored evidence from an Indonesian tertiary centre, the present work helps to redress this imbalance and offers a template-consecutive sampling, validated locally adapted instruments, masked assessment and comprehensive statistical treatment-that other regional services could adopt to generate comparable data. Cumulatively, such studies could support the development of regionally calibrated seizure-adequacy standards suited to the practical realities of ECT delivery in these settings.

Finally, the novelty of the study lies in its direct linkage of a single, intra-procedurally available neurophysiological metric to a validated psychotic-symptom outcome in schizophrenia, a combination that is rare in the existing literature. Whereas most amplitude and electric-field research has been conducted in mood disorders and has used antidepressant or cognitive endpoints, our work demonstrates that the amplitude-response principle extends to the psychotic domain and to the specific symptom clusters that dominate schizophrenia. This extension is not merely incremental: it repositions a familiar bedside observation as a candidate predictive biomarker for one of psychiatry's most disabling conditions, and it does so in a population and health system where the practical payoff of such a biomarker is especially high.[3,11,12]

In summary of the interpretive thread, the present analysis converts an observation long familiar to ECT practitioners-that some seizures simply look more robust than others-into a quantified, reproducible and clinically actionable relationship with symptomatic outcome in schizophrenia. The consistency of the signal across paired within-group comparisons, between-group contrasts, continuous correlation, multivariable adjustment and ROC classification is difficult to reconcile with chance or confounding and instead points to ictal amplitude as a meaningful expression of therapeutic seizure quality. Situated within an Indonesian tertiary psychiatric hospital and a national residency-training network, these results offer both a mechanistic insight and a practical, low-cost lever for improving the care of patients with severe schizophrenia, provided that the causal and longitudinal questions they raise are pursued in appropriately designed prospective studies.

Finally, the results should be interpreted in the context of the evolving evidence on magnetic seizure therapy and other focally targeted convulsive treatments, which aim to reproduce the therapeutic seizure of ECT while limiting the spread of the induced field and its cognitive cost. Comparative trials in schizophrenia report broadly similar PANSS reductions for magnetic seizure therapy and ECT, with structural and neuroplastic correlates that parallel those seen after ECT. Within this landscape, a validated ictal-amplitude criterion is attractive precisely because it is modality-agnostic: it indexes the biological adequacy of the induced seizure irrespective of how that seizure was elicited, and could therefore be transferred to newer neuromodulatory techniques as they enter routine schizophrenia care.[15]

Strengths

The principal strengths of this study include its grounding in real-world tertiary psychiatric practice within an experienced residency-training network, the use of a validated, Indonesian-adapted PANSS administered by trained, masked raters with high inter-rater reliability (ICC=0.86), a pre-specified sampling and analysis plan reported per STROBE, and a comprehensive statistical treatment that moves beyond simple group comparison to include correlation, ROC analysis and multivariable adjustment with effect sizes and confidence intervals throughout. The convergence of these independent analyses on the same conclusion strengthens confidence in the amplitude-response relationship.

Limitations

Several limitations temper interpretation. First, the analytical, non-randomised design means that ictal amplitude was observed rather than manipulated, so residual confounding cannot be excluded and causality

cannot be definitively established, although baseline comparability and multivariable adjustment mitigate this concern. Second, the modest single-centre sample (n=36) limits generalisability and precision, as reflected in the width of some confidence intervals, and warrants replication in larger, multi-centre cohorts. Third, pharmacological confounders-antipsychotic type, dose and the use of agents that alter seizure threshold-were documented but not exhaustively modelled and may influence both ictal amplitude and PANSS change. Fourth, outcomes were limited to short-term PANSS change across a single ECT course without longitudinal follow-up, so the durability of benefit and the relationship of amplitude to relapse remain unknown. Finally, amplitude was analysed as a single peak metric; integrating complementary ictal indices such as post-ictal suppression, mid-ictal slow-wave power and morphology may yield a more complete model of seizure quality and should be a priority for future work.

5. Conclusion

In schizophrenia inpatients undergoing ECT at a tertiary psychiatric hospital in Surakarta, higher peak ictal EEG amplitude was independently associated with substantially greater PANSS improvement. Seizures with amplitude ≥1000 μV produced an additional 11.5-point PANSS reduction (p=0.0004; Cohen d=1.30) and a more than fourfold higher rate of clinically meaningful response, amplitude correlated strongly with symptomatic gain (r=0.73), and it discriminated responders with high accuracy (AUC=0.88; adjusted OR for response 4.85). These findings identify ictal EEG amplitude as an objective, immediately available marker of therapeutic seizure quality that could be used to optimise ECT dosing in schizophrenia, particularly in resource-constrained Indonesian psychiatric practice. Prospective, randomised, multi-centre studies with longitudinal follow-up and integrated multi-parameter ictal analysis are needed to confirm causality and to develop validated, evidence-based models for predicting and enhancing ECT response.

6. References

1. Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. Lancet. 2022;399(10323):473-486. doi:10.1016/S0140-6736(21)01730-X.
2. Solmi M, Seitidis G, Mavridis D, et al. Incidence, prevalence, and global burden of schizophrenia: data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. Mol Psychiatry. 2023;28(12):5319-5327. doi:10.1038/s41380-023-02138-4.
3. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137-150. doi:10.1016/S2215-0366(21)00395-3.
4. Mishra BR, Agrawal K, Biswas T, et al. Comparison of acute followed by maintenance ECT vs clozapine on psychopathology and regional cerebral blood flow in treatment-resistant schizophrenia: a randomized controlled trial. Schizophr Bull. 2022;48(4):814-825. doi:10.1093/schbul/sbac027.
5. Eisenberg DP, Blackman RK, Tietcheu MG, et al. Genetic risk for treatment-resistant schizophrenia and corresponding variation in dopamine synthesis capacity and D2/3 receptor availability in healthy individuals. Mol Psychiatry. 2024;30(6):2645-2652. doi:10.1038/s41380-024-02873-2.
6. Wang Y, Fang X, Wang G, et al. The association between inflammation and kynurenine pathway metabolites in electroconvulsive therapy for schizophrenia: implications for clinical efficacy. Brain Behav Immun. 2023;113:1-11. doi:10.1016/j.bbi.2023.06.016.
7. Grover S, Sarkar S, Sahoo S. Augmentation strategies for clozapine resistance: a systematic review and meta-analysis. Acta Neuropsychiatr. 2023;35(2):65-75. doi:10.1017/neu.2022.30.
8. Yeh TC, Correll CU, Yang FC, et al. Pharmacological and nonpharmacological augmentation treatments for clozapine-resistant schizophrenia: a systematic review and network meta-analysis with normalized entropy assessment. Asian J Psychiatr. 2022;79:103375. doi:10.1016/j.ajp.2022.103375.
9. Melzer-Ribeiro DL, Napolitano IC, Leite SA, et al. Randomized, double-blind, sham-controlled trial to evaluate the efficacy and tolerability of electroconvulsive therapy in patients with clozapine-resistant schizophrenia. Schizophr Res.

2023;268:252-260. doi:10.1016/j.schres.2023.11.009.

10. Zhang R, Yin W, Wang Z. The efficacy and safety of risperidone combined with modified electroconvulsive therapy in the treatment of schizophrenia. Pak J Med Sci. 2025;41(10):2857-2863. doi:10.12669/pjms.41.10.12716.
11. Wang P, Liu C, Zhu X, et al. A clinical control study of modified electroconvulsive therapy and sodium valproate as enhancement strategies for ultra-treatment-resistant schizophrenia. Schizophr Res Cogn. 2025;43:100396. doi:10.1016/j.scog.2025.100396.
12. Dilopoulos I, Nickl-Jockschat T, Grozinger M. Ictal electroencephalography and heart rate as treatment criteria in electroconvulsive therapy: a systematic review of the literature. Eur Arch Psychiatry Clin Neurosci. 2026. doi:10.1007/s00406-026-02298-8.
13. de Arriba-Arnau A, Dalmau Llitjos A, Soria V, et al. Factors predicting ictal quality in bilateral electroconvulsive therapy sessions. Brain Sci. 2021;11(6):781. doi:10.3390/brainsci11060781.
14. Shen T, Yin X, Zhang Y, et al. Seizure adequacy and safety of remimazolam in electroconvulsive therapy for patients with psychiatric disorders: a double-blind randomized crossover trial. BMC Psychiatry. 2026;26:517. doi:10.1186/s12888-026-08202-x.
15. Abbott CC, Miller J, Farrar D, et al. Amplitude-determined seizure-threshold, electric field modeling, and electroconvulsive therapy antidepressant and cognitive outcomes. Neuropsychopharmacology. 2024;49(4):640-648. doi:10.1038/s41386-023-01780-4.
16. Li J, Zhang X, Jiang J, et al. Comparison of electroconvulsive therapy and magnetic seizure therapy in schizophrenia: structural changes/neuroplasticity. Psychiatry Res. 2022;312:114523. doi:10.1016/j.psychres.2022.114523.
17. Li J, Wang J, Yang Y, et al. The effect of electroconvulsive and magnetic seizure therapy on cortical thickness in schizophrenia. CNS Neurosci Ther. 2025;31(3):e70309. doi:10.1111/cns.70309.
18. Geck S, Roithmeier M, Buhner M, et al. COSMIN systematic review and meta-analysis of the measurement properties of the Positive and Negative Syndrome Scale (PANSS). EClinicalMedicine. 2025;82:103155. doi:10.1016/j.eclinm.2025.103155.
19. Findling RL, Youngstrom EA, McClellan JM, et al. An optimized version of the Positive and Negative Symptoms Scale (PANSS) for pediatric trials. J Am Acad Child Adolesc Psychiatry. 2023;62(4):427-434. doi:10.1016/j.jaac.2022.07.864.
20. Jorgensen A, Gronemann FH, Rozing MP, et al. Clinical outcomes of continuation and maintenance electroconvulsive therapy. JAMA Psychiatry. 2024;81(12):1207-1214. doi:10.1001/jamapsychiatry.2024.2360.