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ORIGINAL PAPER

Meta-analysis of initial seizure thresholds in electroconvulsive therapy

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Abstract In electroconvulsive therapy (ECT), electrical dosage is determined using 'fixed-dose', 'age-based' dose, or empirical titration methods. Estimation of initial seizure threshold (IST) has been claimed to be imperative for suprathreshold dosing. This systematic review aimed to determine common levels of IST, to define cut-off values for high IST, and to summarize reported IST associated factors. Medline and PsycINFO were searched from 1966 to January 2008 and relevant references were cross-checked. Subject headings including ECT, seizure threshold, dosage, and dosing were used. All articles reporting on levels of IST and/or associated factors were included. Of 395 potentially relevant reports, 46 studies on 70 samples concerning 3,023 patients were selected. Nine samples ($n = 306$ patients) without available standard deviation and four samples ($n = 275$ patients) treated with mixed electrode placement were excluded. Meta-analysis was done on 30 unilaterally treated samples ($n = 1{,}326$ patients) and 27 bilaterally treated samples ($n = 1{,}116$ patients). In unilateral ECT, weighted mean of IST was 68.2 milliCoulombs (mC; 95% CI 63.2–73.3 mC), and in bilateral ECT 111.6 mC (95% CI 103.7–119.4 mC). Calculated cut-off values for high IST were 121 mC for unilateral ECT and 221 mC for bilateral ECT. According to the literature, male gender and use of bilateral electrode placement appeared to increase IST most prominently. In conclusion, calculated electrical doses for 'suprathreshold' right unilateral ECT and for 'moderate above threshold' bilateral ECT, using commonly reported IST levels, were in the same though narrower ranges as provided in 'fixed-dose' and 'half-age' based strategies, respectively.

Keywords Meta-analysis · (Initial) seizure threshold · ECT

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Introduction

Electroconvulsive therapy (ECT) is an important treatment option for patients with severe, psychotic, or pharmacotherapy-resistant mood disorders [1, 3]. To be effective, seizure activity has to be elicited, and the minimal electrical stimulus in the first treatment session that provokes a generalized seizure of sufficient duration indicates the initial seizure threshold (IST) [1, 3]. In the literature, different seizure durations define seizure adequacy and no systematic association has been shown between seizure duration and clinical improvement [1, 2, 13]. Clinicians use different methods to choose the initial stimulus dose, of which 'age-based' [2], 'half-age-based' [47], 'fixed-high' [1, 38] and 'empirical titration-based' dosing strategies are common.

Controversy, however, exists about the ability of these different methods to determine the optimal stimulus dose and their risk-benefit ratios [2, 17, 18, 21, 68]. For example, in unilateral ECT it has been claimed that the electrical stimulus has to exceed the IST substantially for optimal effectiveness (e.g. 6–12 times above IST) [38, 59]. Moreover, seizure thresholds appear to vary substantially among patients [2], and factors as gender [53], age [55], previous ECT treatment and concomitant medication usage [1, 54] may influence seizure thresholds. Some patients show

exceptionally high IST being associated with an increased risk of subconvulsive stimulation and unilateral ECT failure [67].

These findings may imply that basic measurement of the IST by titration protocols would be favourable above other methods. Others, though, stated that in the vast majority of patients the distribution of IST would be tightly clustered in the 50–200 milliCoulombs (mC) range, and therefore the proper electrical dose should be accomplished without dose titration [2, 27]. Thus for clinicians, knowledge about the common IST level in average patients may be useful to decide on the preferred stimulus dosing method. Therefore, the aim of our study was to analyse studies on IST and to determine whether common IST levels for both unilateral and bilateral ECT could be possibly deduced from these data. We also wanted to define cut-off values for high IST, since these patients may pose a special problem for clinicians. Additionally, we aimed to summarize reported factors that may be associated with IST levels.

Methods

This review aimed to include all published articles on IST in ECT. Medline (Pubmed, National Library of Medicine, http://www.ncbi.nlm.nih.gov) and PsycINFO (American Psychological Association 2008) were searched for articles that were published from 1966 to January 2008. The abstracts of the 395 retrieved articles were examined for information on IST (Fig. 1). Of these articles, 348 were excluded because they did not report on IST and one because the reported mean IST was extraordinarily high compared to those reported in the other studies [50]. References of the remaining 46 articles were cross-checked, and three standard works on ECT were examined as well [1, 3, 13]. The 46 studies that were selected for further investigation consisted of 70 patient samples; 34 patient samples were treated with unilateral ECT, 32 with bilateral ECT and 4 with mixed electrode placement. Because electrode placement is known to have a substantial influence on seizure thresholds [55], mixed samples were excluded ($n = 4$; 275 patients). Furthermore, nine samples (306 patients) could not be used in the meta-analysis because standard deviations of the mean IST were lacking. Therefore, 57 samples containing 2,442 patients were available for further investigation. These studies were scrutinized for: (1) patient characteristics such as age, gender, psychiatric diagnosis, use of anticonvulsants and previous ECT; (2) treatment characteristics such as electrode placement, settings of the device (constant-current and pulse width), titration process including seizure duration and definition of an adequate seizure, and the anaesthetic drugs used; and (3) data on IST [mean and standard deviation (SD), or median and range in mC] in both unilateral and bilateral ECT.

Statistics

Data are presented as numbers and percentages, and means and SD or medians and interquartile ranges (IQR) when appropriate, using SPSS for Windows (version 13.0). After meta-analysis of the data on mean IST with the statistical package of Comprehensive Meta-Analysis (version 2.0), forest plots were generated. Because the included studies proved to be substantially heterogeneous, random effect models were used. Furthermore, we defined high IST level as the upper high 95% bound of the mean IST, which was calculated by adding two times the SD to the mean IST of each patient sample. For both unilaterally and bilaterally treated samples the medians and IQR of these cut-off values were calculated.

Results

Patient and treatment characteristics of the samples

Table 1 summarizes the patient and treatment characteristics of the samples included in the meta-analysis. Mean age of the 57 samples ($n = 2442$ patients) ranged from 29.8 to 73.8 years, and 36.9% of the patients were male. Most samples concerned patients with major depression ($n = 37$; 64.9%). In 22 (38.6%) samples, also patients with bipolar depression were included. In most studies, seizure adequacy was defined as visible motor activity (35.1%) or EEG seizure activity (22.8%) with a duration $\geq$25 s. All studies, except one [4], described the use of ECT devices with constant-current and brief pulse properties. In most cases (52 samples; 91.2%), a barbiturate (methohexital or thiopental) was administered as anaesthetic.

Levels of IST (Table 1)

The means and ranges of reported IST were analysed in two ways. Using Comprehensive Meta-Analysis software (random effects model), the weighted overall mean IST in right unilateral ECT was 68.2 mC [standard error 2.59; 95% confidence interval (CI) 63.2–73.3 mC], and in bilateral ECT 111.6 mC (standard error 4.02; 95% CI 103.7–119.4 mC). Figure 2 presents these findings in a forest plot.

In the unilaterally treated samples, the means of IST ranged from 42.7 to 138.9 mC (median of all means 66.6 mC, IQR 58.4–78.1 mC), and in bilaterally treated samples from 63.8 to 192.3 mC (median of all means 107.5 mC, IQR 94.8–130.0 mC). The cut-off values for high IST in the unilaterally treated samples ranged from 59.3 to

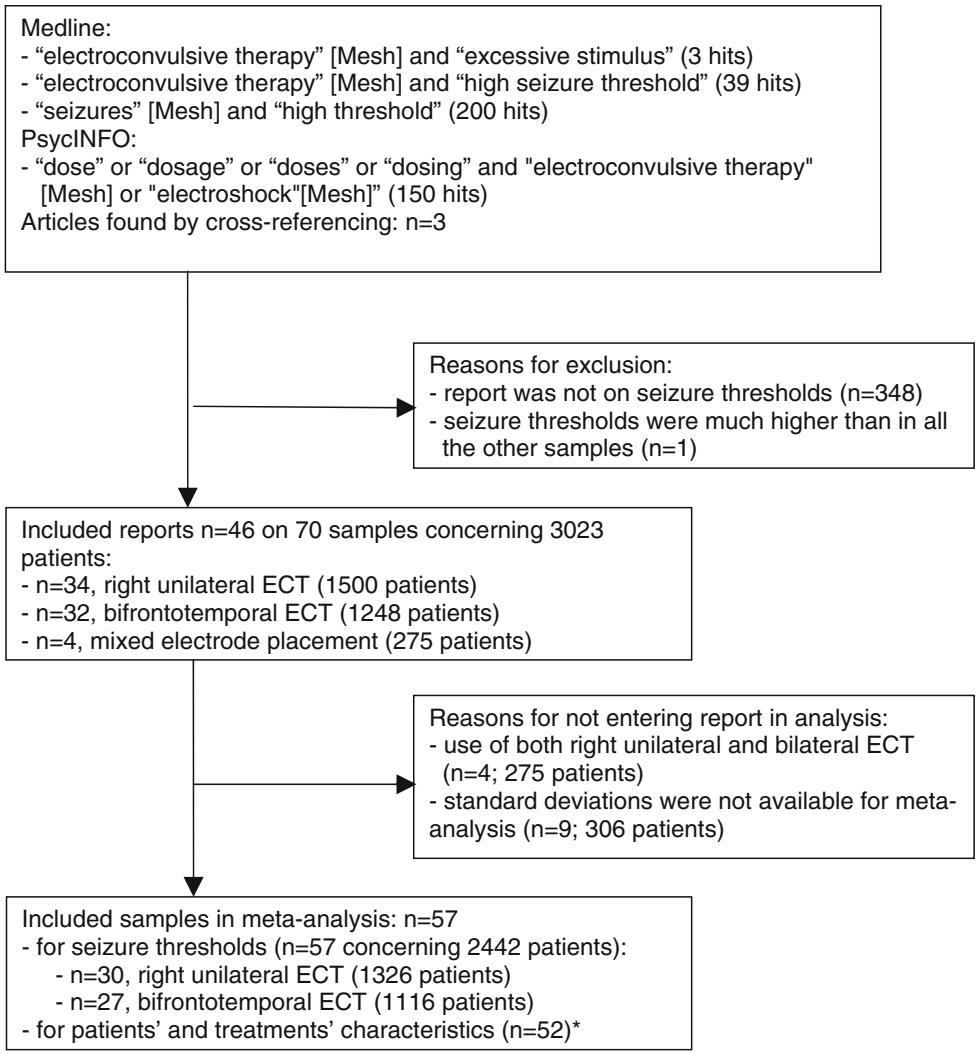

Fig. 1 Flow diagram of selection of reports on initial seizure threshold in ECT

* For 5 samples the characteristics of patients and treatments were not reported.

281.5 mC (median 120.9 mC, IQR 104.1–163.5 mC); and in the samples treated with bilateral ECT from 119.9 to 499.9 mC (median 221.0 mC, IQR 161.8–285.5 mC).

Determinants of IST

In the reviewed literature, several patient-related, treatment-related and some miscellaneous factors were shown or mentioned to be possibly associated with the level of IST (Table 2). When taking into account prospective studies only, levels of IST were significantly related to the following factors: gender [53], age [53], number of cumulative treatments [53, 61], electrode placement [58], dynamic impedance [15], current characteristics such as stimulus train duration, frequency, pulse width, and amperage [20, 29], and sleep deprivation [19]. Male gender [53] and bilateral electrode placement [58] were reported to increase IST most prominently.

Discussion

We found that the overall mean of IST in the 30 patient samples treated with right unilateral ECT was 68.2 mC (95% CI 63.2–73.3 mC), whereas in the 27 patient samples that received bilateral ECT the overall mean was 111.6 mC (95% CI 103.7–119.4 mC). IST might be considered as high when the electrical stimulus has to exceed 121 mC in unilateral ECT or 221 mC in bilateral ECT to induce a generalized seizure of at least 25–30 s on EEG. Of reported factors associated with IST levels, male gender and bilateral electrode placement predicted higher IST most explicitly.

Clinical relevance of these findings

Although in the literature, IST levels were suggested to vary substantially between individual patients justifying the empirical titration as a more accurate dosing method (e.g. a

Table 1 Characteristics of patients and treatment in all the study samples ($n = 57$ concerning 2,442 patients)

Mean age (±SD, range) in years	51.7 (±9.1, 29.8–73.8)
Male[a]	971 (36.9%)
Psychiatric diagnosis[a] (%)	
Major depression	37 (64.9)
Bipolar depression as well	22 (38.6)
Psychosis	3 (5.3)
Various diagnoses	13 (22.8)
Not described	4 (7)
Exclusion criterion used[a] (%)	
Use of anticonvulsants	42 (73.7)
ECT in previous 6 months	41 (71.9)
Definition of seizure adequacy in seconds (s)[a] (%)	
Visible motor seizure activity ≥25 s	20 (35.1)
EEG seizure activity ≥25 s	13 (22.8)
Visible motor seizure activity ≥15 s	11 (19.3)
Visible motor seizure activity ≥30 s	3 (5.3)
Other description	2 (3.5)
Not described	8 (14)
Settings of ECT device[a] (%)	
Constant current 0.8 Ampere (Å)	27 (47.4)
Range of used currents in studies	0.55–0.9 Å
Brief pulse 1.0 ms	20 (35.1%)
Range used pulse width in studies	0.5–2.0 ms
Anaesthetic used[a] (%)	
Methohexital	36 (63.2)
Thiopental	16 (28.1)
Other anaesthetic (etomidate; propofol; or not specified)	2 (3.5)
Not described	3 (5.3)
Values of IST in unilateral treated patient samples ($n = 30$)	
Range of IST values	42.7–138.9 mC
Median IST	66.6 mC (IQR 58.4–78.1 mC)
Weighted mean in meta-analysis	68.2 mC (95% CI 63.2–73.3 mC)
Cut-off values for high IST in unilateral treated patient samples ($n = 30$)	
Range of high IST values	59.3–281.5 mC
Median of high IST values	120.9 mC (IQR 104.1–163.5 mC)
Values of IST in bilateral treated patient samples ($n = 27$)	
Range of IST values	63.8–192.3 mC
Median IST	107.5 mC (IQR 94.8–130.0 mC)
Weighted mean in meta-analysis	111.6 mC (95% CI 103.7–119.4 mC)
Cut-off values for high IST in bilateral treated patient samples ($n = 27$)	
Range of high IST values	119.9–499.9 mC
Median of high IST values	221.0 mC (IQR 161.8–285.5 mC)

SD standard deviation, *EEG* electroencephalogram, *IST* initial seizure threshold, *IQR* interquartile ranges, *mC* milliCoulombs

[a] Data are in numbers and percentages unless otherwise indicated

35-fold range; [6]), this meta-analysis showed a more narrow range of mean IST. The IST levels, as found in this meta-analysis, bring together the concepts of 'dose-titration', 'fixed-dose' and 'half-age' methods, which was suggested before by rough clinical estimations [27]. After all, a calculated dose for suprathreshold unilateral ECT [59] using our calculated weighted mean IST (e.g. 6×68.2 mC $\approx$ 409 mC) corresponds to the stimulus dose range as advocated in 'fixed-dose' methods (378–504 mC) for both unilateral and bilateral ECT [2]. On the other hand, the found IST level of 111.6 mC used in 'moderate above IST bilateral stimulus dose' calculations (e.g. $1.5–2.5 \times 111.6$ mC $\approx$ 167–279 mC) suggests that the use of 'fixed-dose' methods (378–504 mC; [2]) may result in overstimulation, and corresponds more to the 'half-age' method stimulus dose range (50–252 mC) in bilateral ECT [47].

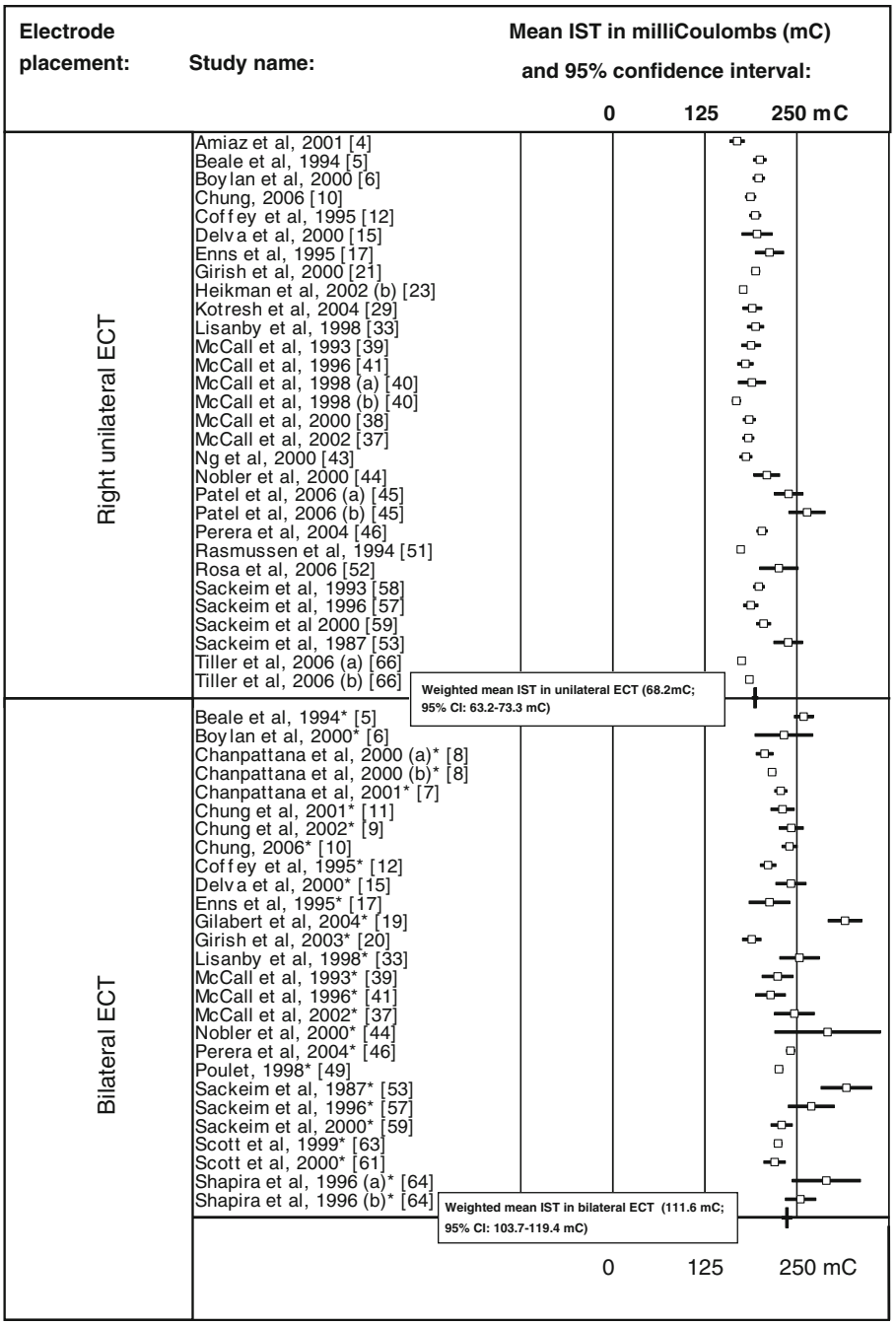

Fig. 2 Forest plot of meta-analysis of initial seizure thresholds (IST) in electroconvulsive therapy ($n = 30$ right unilaterally treated samples concerning 1,326 patients, and $n = 27$ bilaterally treated samples concerning 1,116 patients)

Strengths and limitations

Although our systematic literature review is relatively complete, only cautious conclusions may be drawn. IST levels were collected from studies that did not primarily aim to examine IST and its associated factors, and the selected samples could not be stratified for gender or for other presumed influencing factors as many data on the 2,442 individuals studied were lacking. This may have influenced our results. For example, if samples would contain relatively more males, or more subjects with lower dynamic impedances, or if IST increasing current characteristics (shorter stimulus train duration, higher stimulus frequency, longer pulse width, lower amperage) were used, the weighted mean would be higher than real. Furthermore, in 22 samples (38.6%) seizure thresholds were analysed in patients with unipolar as well as bipolar depressive disorders together. Since it has been suggested that patients with bipolar disorder may have a lower seizure threshold [42], inclusion of these patients may have decreased the overall means of IST. Also, patients who could not reach adequate seizure durations most probably have been excluded,

Table 2 Possible determinants for initial seizure thresholds (IST) in electroconvulsive therapy (ECT)

Determinant	Type of influence
Patient characteristics	
Gender[a]	Men have much higher IST (approximately 70%) than women [53]
Age[a]	Moderate association, somewhat sex dependent: elderly men have highest IST [53]
Racial diversity	African-Americans may have higher IST [14]
Some morphological characteristics	Thickness of skin and scalp bone, and higher brain density may raise the IST, probably due to a raise of static impedance [64]
Longer inion-nasion distances	Wider interelectrode (inion-nasion) distance may be associated with higher IST, especially in women [14, 39]
Body-mass index (BMI)	In Chinese patients, higher BMI was associated with higher IST [10]
Presence of neurodegenerative disorder	In dementia, there may be an additional decrease in neuronal excitability associated with higher IST [31]
Greater medical burden	Modest association with higher IST, especially in patients with cardiovascular diseases [6]
Psychiatric diagnosis	Manic patients may have lower IST than depressed patients [42]
Use of psychotropic drugs	
Anaesthetic drugs	Thiopental may have a disadvantage over etomidate in producing seizures of adequate duration [28]
Anticonvulsants	Higher stimulus doses are required to overcome IST [1]
Benzodiazepines	Average lorazepam dosage in 48 h before ECT was not associated with higher IST, but with decreased seizure duration [6]
Barbiturates	Have anticonvulsant properties [6]
Neuroleptics	May have an inverse effect and be associated with a lower IST [48]
Beta-blockers	May raise IST; atenolol does not pass the blood-brain barrier, but metoprolol and propranolol do [35]
Calcium-antagonists	May raise IST [16]
Lidocaine	Shortens seizures and may raise IST [13]
ECT characteristics	
Cumulative number of treatments[a]	Average of 65% increase in IST from first to final session of ECT course [53, 61]
Electrode placement[a]	IST is higher in bilateral than in right unilateral ECT, and increased on average by 87% during bilateral treatment, and only 40% during right unilateral ECT [53]
Dynamic impedance[a]	Lower dynamic impedance increased IST [56]
Current[a]	Shorter stimulus train duration with same dose increased IST [20]
	Higher stimulus frequency (pulses per second) increased IST [20]
	Longer pulse width increased IST [29, 60]
	Stimuli of 0.8 Å gave higher IST than stimuli of 0.9 Å [65]
Miscellaneous factors	
Sleep deprivation[a]	Decreased IST [19]
Drinking alcohol	May increase IST [26]

[a] Results of prospective study

leading to underestimation of the seizure threshold. In only one study, however, this was mentioned as an exclusion criterium [51].

Moreover, the lack of a standardized definition of adequate seizure duration in titration protocols hampered appropriate comparison of studies. In 40% of the studies, minimal duration of 25–30 s of 'visible motor seizure activity' was assumed to be adequate, which is rather arbitrary [1, 2]. In more than 19% of the studies, a shorter seizure duration was regarded as adequate. Limiting our meta-analysis though to the studies that defined an adequate seizure duration as ≥25 s of 'visible motor seizure activity' revealed, however, comparable weighted means of IST (unilateral ECT $n = 27$; mean 68.2 mC; 95% CI 62.8–73.6 mC; bilateral ECT $n = 19$; mean 107.1 mC; 95% CI 97.8–116.3 mC). Seizure duration monitoring was sometimes performed with the cuff-method only, which is probably unreliable and might lead to higher estimation of IST as the seizure duration would sometimes be incorrectly regarded as insufficient [36]. Further research on IST could be optimized using standardized procedures for seizure duration monitoring and an agreed definition for seizure adequacy in the titration protocols.

Finally, the calculated levels of mean IST will probably be applicable in most patients, but some individuals will have lower or higher IST, which in unilateral ECT might

result in over- or understimulation. Although some factors are known to influence IST, it is uncertain in what manner these must be taken into account in determining IST for the individual patient.

In conclusion, based on this meta-analysis, an IST of 68.2 mC for the calculation of suprathreshold unilateral ECT is within the stimulus dose range of 'fixed-dose' methods. A 'moderate above IST bilateral ECT stimulus' dose, calculated with an IST of 111.6 mC, is substantially lower than the stimulus dose range of 'fixed-dose' methods but is within the 'half-age method' based dose range. Given the discussion in the literature about optimal dosing strategies, these findings support use of 'fixed' and 'half-age' methods. Male gender and bilateral electrode placement were reported to increase IST most prominently, and IST exceeding 121 mC in unilateral ECT and 221 mC in bilateral ECT may be regarded as high. More research is needed to determine the relevance of factors influencing IST.

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Conflict of interest statement The authors declare that they have no conflicts of interests.

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