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Etomidate improves seizure adequacy during electroconvulsive therapy

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ABSTRACT

The purpose of this study was to assess whether switching propofol to etomidate during an electroconvulsive therapy course improves seizure quality in convulsion-resistant patients. A retrospective study of paired cases included thirty-three patients. Seizure variables for each agent were assessed. A generalized linear mixed model (GLMM) for repeated measures was used for the analysis. Anesthesia with etomidate leads to greater seizure duration, improved seizure quality in the EEG register, and prevents further need for restimulation; although did not differ from propofol in the amount of energy delivered or in other automated parameters. These results suggest that this procedure appears to be an adequate strategy to improve seizure quality.

1. Introduction

In order to achieve a clinical response to treatment during a course of electroconvulsive therapy (ECT), proper seizure duration (Dunne and McLoughlin, 2013) and electroencephalogram (EEG) recording (Rattehalli et al., 2009; Scott and Waite, 2013) must be obtained. Traditionally, an adequate seizure is considered to have a minimal duration of 25 s in the EEG (Krystal, 2010), an EEG record in which the seizure develops well morphologically (Abrams, 2002; Azuma, 2009; Rattehalli et al., 2009). Anesthesia is a factor that influences the quality of the seizure, but there are no guidelines on how to select the anesthetic agent or its change during ECT (Hoyer et al., 2014). Although in our environment propofol is generally used (Martínez-Amorós et al., 2015), there are authors who observe an unfavorable effect of propofol on the quality and duration of the seizure (Hoyer et al., 2014; Simpson et al., 1988; Vaidya et al., 2012; Hooten and Rasmussen, 2008), whereas others do not (Caliyurt et al., 2004; Canbek et al., 2015) or find there is no clinical significance (Bauer et al., 2009; Eranti et al., 2009; Eser et al., 2010; Fear et al., 1994; Grati et al., 2005; Mitchell et al., 1991). With "resistance to convulsion", the change to etomidate can prolong its duration (van Waarde et al., 2009a; Hooten and Rasmussen, 2008; Eranti et al., 2009).

According to some authors (Petrides et al., 2009; van Waarde et al., 2009b), the delivery of electrical doses above 40% of the stimulus energy should be considered excessively high; in our ECT unit we switch the anesthetic in order to avoid this dose increase.

The aim of this study was to assess whether switching the anesthetic agent is an appropriate strategy for improving seizure quality in difficult seizure elicitation.

2. Methods

A retrospective study of paired cases was conducted with patients who first received propofol for anesthesia induction during an ECT course and then switched to etomidate.

2.1. Patients

All patients were recruited from the ECT unit of the Psychiatry Department of the Hospital General de Granollers - Benito Menni CASM from July 2009 to July 2017 and gave written consent to the use of their data for research purposes.

Data were obtained by reviewing a total of 230 medical records, from which 63 patients met the inclusion criteria: 30 patients were excluded for different reasons (four for program change during treatment, four for change of electrode position during the course of ECT, ten for change of session frequency, five for combining etomidate and propofol in the same session, seven for lack of data) and 33 patients were included in the final sample. Diagnoses were encoded according to DSM-IV-TR (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision) criteria (López-Ibor and Valdés, 2002).

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2.2. The ECT procedure

A Thymatron System IV (Class 1, Type BF, Somatics LLC, USA) was used for performing the ECT. Propofol was used for anesthetic induction (mean dose = 70.53 mg, SD = 16.08; 0.97 mg/kg, SD = 0.17) prior to the switch to etomidate (mean = 9.03, SD = 1.67 mg; 0.12 mg/kg, SD = 0.26). Succinylcholine was used as a muscle relaxant and atropine was used optionally. Stimulus dose was calculated according to the "age method". The change to etomidate took place when an electrical dose of the stimulus ≥40% (201.6 mC) did not achieve an adequate seizure (it was mainly considered that it had a duration <25 s in the EEG, but also that the record was of poor quality: low ictal amplitude, indeterminate ending point, no development of the characteristic phases). Thus, not all patients received the same number of sessions with propofol or with etomidate. A maximum of two restimulations were delivered in each session, usually increasing the dose delivered by 10% in the first stimulation and using 100% energy in the second restimulation.

For statistical analysis, only the energy and seizure parameters of the latest stimulation were considered, and the succinylcholine and atropine doses correspond to the total sum of doses administered during all stimulations. Bifrontotemporal (BL) electrode placement for stimulus delivery was used in 29 patients, and LART (Left Anterior Right Temporal) for 4 patients. A brief pulse (bidirectional, square-wave 0.5 ms pulse width) was used in all patients. Electrodes for EEG were placed in both mastoid regions and a third one in the middle frontal region. Pulse oximetry, blood pressure and ECG register were monitored.

2.3. Assessments

Sociodemographic data, concomitant use of drugs (antidepressant, antiepileptic, antipsychotics, lithium, benzodiazepines, flumazenil or opioids), stimulus energy, EEG seizure duration, number of restimulations and automated parameter values – average seizure energy index (ASEI), postictal suppression index (PSI), maximum sustained coherence (MSC), and peak heart rate (pHR)- were assessed.

For a seizure to be considered appropriate, its duration should be ≥25 s, with ASEI ≥ 550 μV^2, PSI ≥ 80%, MSC ≥90% and pHR > 140 bpm. A visual rating of EEG quality was also performed by considering the presence of the characteristic EEG phases (hypersynchronous polyspikes, polyspike-and-slow wave and postictal supression), assigning one point for each phase present (following the assessment similar to that proposed by Rattehalli).

2.4. Statistical analysis

For sample characterization, descriptive statistics (mean, standard deviation and frequency) were used; $P \leq 0.05$ was considered statistically significant. A Kolmogorov–Smirnov test was performed to examine the distribution of variables, Student's *t*-test for categorical variables and χ^2 test for sociodemographic data, automated parameters and proper EEG seizure duration. Assessment of the number of restimulations and continuous variables was performed by Fisher's exact test due to the small sample size. To appraise the energy delivered throughout the course of the ECT sessions and the seizure quality in the EEG phases, considering that repeat measurements were performed for each subject but a different number of measurements were made across different subjects (unbalanced design), two GLMM for repeated measures were used for the analysis: one to analyze the energy count and the other for the quality of the convulsion. In these models, age, sex, treatment and time were established as fixed effects; each subject was considered as a random effect. Owing to the small sample size, a restricted maximum likelihood (REML) estimator was used. SPSS Statistics 24 software was used for statistical analysis (IBM Corp, 2016).

Table 1
Sociodemographic and clinical characteristics of the sample.

Age mean (SD)	57.7 (14.7)
Sex *n* (%)	
Male	10 (30.3)
Female	23 (69.7)
Diagnosis *n* (%)	
MDD psychosis	8 (24.2)
MDD resistant	10 (30.3)
BPD mania	3 (9.1)
BPD depression	3 (9.1)
Schizoaffective disorder	6 (18.2)
Oher	3 (9.1)
GAF baseline mean (SD)	42.6 (12.1)
GAF final mean (SD)	64.6 (8.8)
ECT administration *n* (%)	
Hospitalized	30 (90.9)
Outpatient	3 (9.1)
ECT sessions mean (SD)	
Propofol	4.9 (2.5)
Etomidate	6.8 (3.3)
ECT sessions frequency (*n*, %)	
3 for week	23 69.7
2 for week	9 27.3
other	1 3.0

MDD, Major Depressive Disorder. BPD, Bipolar Disorder. GAF, Global Assessment Functioning.

3. Results

3.1. Clinical and sociodemographic characteristics of the sample

Characteristics of the sample are shown in Table 1. The included patients improved their initial GAF score by 51.6%.

There were no statistically significant differences among propofol and etomidate groups with the use of psychiatric drugs or succinylcholine and atropine (Table 2).

3.2. Procedure results

As shown in Fig. 1, in the propofol group there was a progressive increase of the energy needed for a proper seizure, whereas this was not seen in the etomidate group.

Only the average energy delivered in the first seven ECT sessions is shown; because only 12.6% of the patients underwent more than seven sessions, it cannot be concluded that the results from Session 8 are representative of all the patients. According to GLMM analysis, subjects in the etomidate group were expected to have 3.73 higher energy counts than those in the propofol group ($F_1 = 13.70$, $P < 0.001$). In the analysis, sex, age and weight are the factors thought to affect the convulsive threshold.

The time of convulsion in the EEG with propofol is shorter than with etomidate and the difference is statistically significant. None of the automated parameters, except the pHR, to distinguish seizure quality among both groups reached statistical significance (Table 2).

The number of restimulations was higher when using propofol ($n = 67$) rather than etomidate ($n = 17$), this difference being statistically significant (Mann–Whitney U test = 171, $P < 0.001$).

Regarding the visual rating of EEG convulsion quality significant differences were found between both groups (Table 2). Following the GLMM model, subjects with etomidate were expected to have a 0.50 less quality convulsion count than those using propofol ($F_1 = 41.43$, $P < 0.001$).

4. Discussion

The results show that switching proprofol to etomidate during ECT in seizure-resistant patients achieves an appropriate seizure through a

Table 2
Concomitant psychiatric drugs and seizure quality parameters. tEEG, electroencephalogram seizure duration in seconds.

	Propofol mean	(SD)	Etomidate mean	(SD)	Statistical analysis Test	p_value
Concomitant use of psychotropic drugs						
Dose						
Succinylcholine	48.55	(7.82)	49.08	(8.44)	T = 0.63	0.52
Atropine	0.45	(0.18)	0.47	(0.14)	T = −1.23	0.22
Dose mg/Kg						
Succinylcholine	0.68	(0.16)	0.68	(0.13)	T = 0	0.99
Atropine	0.0064	(0.0031)	0.0065	(0.0022)	T = −0.37	0.71
	n = 33	%	n = 33	%	Test	p_value
Psychiatric medication						
Antidepressants	25	75.75	27	81.81	Exact Fisher	0.78
Antipsychotics	26	78.78	24	72.72		0.78
Lithium	5	15.15	6	18.18		0.75
Benzodiazepines	29	87.87	25	75.75		0.34
Anticonvulsants	14	42.42	11	33.33		0.46
Flumazenil/opiates	12	36.36	16	48.48		0.46
Characteristics of the convulsion						
tEEG					χ^2 = 31.71	< 0.001
Seconds mean (SD)	29.5	(28.2)	36.8	(15.3)		
< 25 sec	77	51.3	50	22.9		
≥ 25 sec	73	48.7	168	77.1		
ASEI					Fisher's Exact	0.066
microV^2 mean (SD)	7331.3	(6688.8)	8730.4	(16,557.8)		
< 550 microV2	4	3.4	1	0.5		
≥ 550 microV2	113	96.6	196	99.5		
PSI					χ^2 = 0.118	0.73
Percentage mean (SD)	62.7	(25.1)	64.5	(23.4)		
<80%	73	70.2	129	68.3		
≥80%	31	29.8	60	31.7		
MSC					χ^2 = 2.81	0.094
Percentage mean (SD)	84.6	(19.0)	87.4	(17.4)		
<90%	61	45.5	75	36.4		
≥90%	73	54.5	131	63.6		
Heart rate: mean (SD)						
Difference (peak - basal)	22.16	(20.45)	34.60	(20.63)	Z = −5.81	< 0.001
Peak Heart Rate					χ^2 = 17.9	< 0.001
Less than 140 bpm	139	47.1	156	70.9		
More than 140 bpm	17	10.9	64	29.1		
Convulsion Quality						
0	8	5.0	1	0.4	χ^2 = 26.31	< 0.001
1	36	22.5	21	9.4		
2	73	45.6	103	46.2		
3	43	26.9	98	43.9		

longer seizure duration, higher peak heart rate, and a higher quality EEG registry: the two first findings coincide with other studies (Eranti et al., 2009; Grati et al., 2005; Hooten and Rasmussen, 2008; Hoyer et al., 2014; Singh et al., 2015; Wang et al., 2011; Swartz, 2009) but the latter, to the best of our knowledge, has not been explored previously. A higher quality of seizure implies a possible greater effectiveness (though not enough, at least it is a necessary condition for it) and a lower number of restimulations.

Although some studies reported lower PSI when using etomidate (Eser et al., 2010), we did not find any differences among automated parameters when comparing both groups. This may be because of the presence of EEG artifacts or due to the fact that propofol and etomidate were used when the convulsive threshold could be different, as it is known that the convulsive threshold tends to increase along an ECT course.

Consistent with other studies (Eranti et al., 2009), our patients also received a higher number of restimulations with propofol. We did not observe a tendency for an increase of energy dose to be used in the sessions with etomidate induction. Due to the design of the study, the energy dose when etomidate is used is necessarily greater than when using propofol. However, energy dose with etomidate is not increased throughout the sessions as strongly as with propofol, so we could say that the convulsive threshold is not risen as it is when propofol is used. Otherwise, if we take into account that some authors establish that the relationship between the energy increase of stimulus and the duration of the seizure is not linear (even at high doses the duration may be shorter) (Weiner, 2010) and poor seizure morphology is little influenced by increasing the stimulus intensity (Vaughn McCall, 2009), it is unlikely that the positive results found when using etomidate are due to the use of a higher dose of energy. Both of these facts could avoid the appearance of memory impairment (Ingram et al., 2008).

It is unlikely that concomitant medication may have influenced the results, as there were no differences in their use between both groups. Moreover, it has been shown that psychiatric drugs do not affect seizure adequacy during ECT (Bundy et al., 2010).

The main value of our study is its naturalistic nature and the use of low doses of anesthetic agents compared to those recommended (Kellner et al., 2009; Mankad and Weiner, 2010). However, it has limitations: it is a retrospective study and, due to the design used, we cannot prove that switching propofol to etomidate leads to better therapeutic outcomes; it also lacks the neurocognitive assessments.

5. Conclusions

In summary, we can conclude that the change from propofol to etomidate in seizure-resistant patients allows the quality of the seizure to be improved. Although it is an easy and recommendable strategy in this group of patients, further studies are needed to confirm the results.

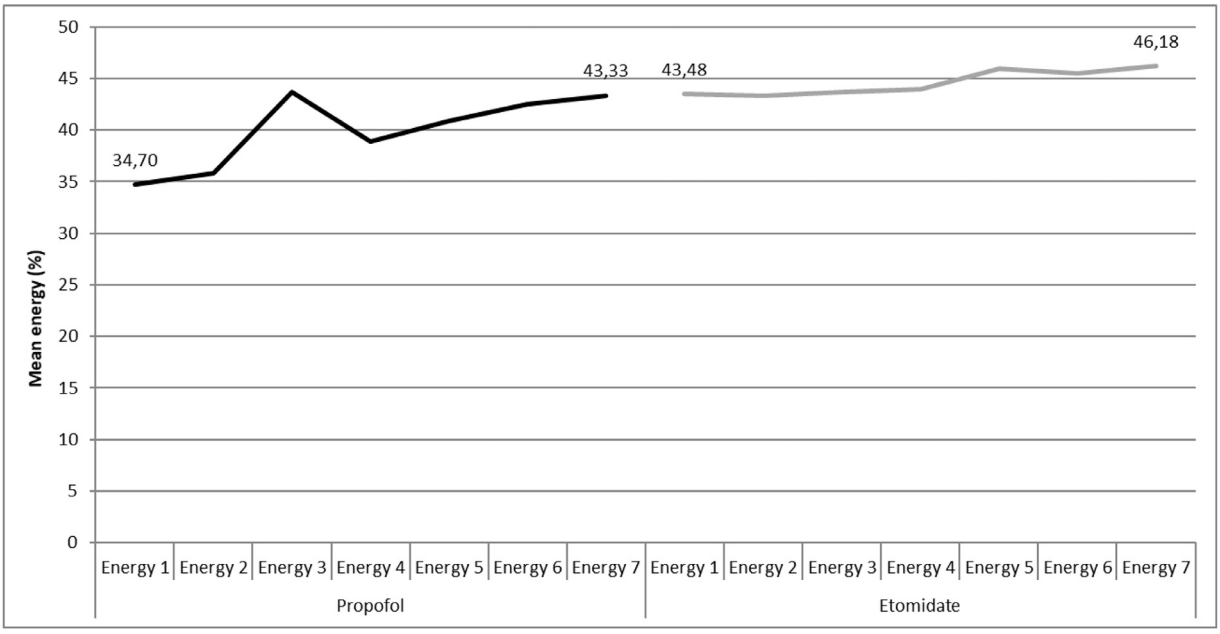

Fig. 1. Comparison of mean energy (expressed as %) used with propofol (black) and etomidate (grey) during ECT course. The mean energy used with propofol at the first session was 34.70% (SD: 18.87), increasing till 43,33% at session 7 (SD: 13.46). On the other hand, when the same patients switch to etomidate, the mean energy used at the first session was 43.48% (SD:11.42), reaching a mean energy of 46.18% (SD: 14.53) at session 7. The difference between the mean energy increase with propofol vs etomidate was not found to be statistically significant.

Declarations of interest

None.

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References

Abrams, R., 2002. The electroconvulsive therapy stimulus, seizure induction, and seizure quality. In: Abrams, R. (Ed.), fourth ed. Electroconvulsive Therapy 101-. Oxford University Press, New York, pp. 129.

Azuma, H., 2009. Electroencephalogram monitoring and implications. In: Swartz, C.M. (Ed.), Electroconvulsive and Neuromodulation Therapies. Cambridge University Press, New York, pp. 468–476.

Bauer, J., Hageman, I., Dam, H., Henrik, D., Báez, A., Bolwig, T., et al., 2009. . Comparison of Propofol and thiopental as anesthetic agents for electroconvulsive therapy. A randomized, blinded comparison of seizure duration, stimulus charge, clinical effect, and cognitive side effects. J. ECT 25 (2), 85–90. https://doi.org/10.1097/YCT.0b013e31818a0203.

Bundy, B.D., Hewer, W., Andres, F-J., Gass, P., Sartorius, A., 2010. Influence of anesthetic drugs and concurrent psychiatric medication on seizure adequacy during electroconvulsive therapy. J. Clin. Psychiatry 71, 775–777. https://doi.org/10.4088/JCP.08mm04971gre.

Caliyurt, O., Vardar, E., Tuglu, C., Ercan, A., 2004. Effects of Propofol on electroconvulsive therapy seizure duration. Can. J. Psychiatry 49, 707–708.

Canbek, O., Ipeckcioglu, D., Menges, O.O., Murat, I.A., Karamustafahoglu, N., Cetinkaya, O.Z., et al., 2015. Comparison of Propofol, etomidate, and thiopental in anesthesia for electroconvulsive therapy. A randomized, double-blind clinical trial. J. ECT 31 (2), 91–97. https://doi.org/10.1097/YCT.0000000000000190.

Dunne, R.A., McLoughlin, D.M., 2013. ECT prescribing and practice. In: Waite, J., Easton, A. (Eds.), The ECT Handbook, third edition. The Royal College of Psychiatrists, Glasgow, pp. 28–44.

Eranti, S.V., Mogg, A.J., Pluck, G.C., Landau, S., McLoughlin, D.M., 2009. Metohexitone, Propofol and etomidate in electroconvulsive therapy for depression: a naturalistic comparison study. J. Affect. Disord. 113, 165–171. https://doi.org/10.1016/j.jad.2008.03.004.

Eser, D., Nothdurfter, C., Schüle, C., Damm, J., Steng, Y., Möller, H-J., et al., 2010. . The influence of anaesthetic medication on safety, tolerability and clinical effectiveness of electroconvulsive therapy. World J. Biol. Psychiatry 11, 447–456. https://doi.org/10.3109/15622970902960897.

Fear, Ch.F., Littlejohns, C.S., Rouse, E., McQuail, P., 1994. Propofol anaesthesia in electroconvulsive therapy reduced seizure duration may not be relevant. Br. J. Psychiatry 165, 505–509. https://doi.org/10.1192/bjp.165.4.506.

Grati, L., Louzi, M., Nasr, K.B., Zili, N., Mansalli, L., Mecbri, A., et al., 2005. Effets comparés de l'étomidate et du Propofol pour l'anesthésie lors de l'électroconvulsivothérapie. Press. Med 34, 282–284.

Hooten, W.M., Rasmussen, K.G., 2008. Effects of general anesthesic agents in adults receiving electroconvulsive therapy: a systematic review. J. ECT 24 (3), 208–223. https://doi.org/10.1097/YCT.0b013e31815bfe2a.

Hoyer, C., Kranaster, L., Janke, Ch., Sartorius, A., 2014. Impact of the anesthetic agents ketamine, etomidate, thiopental, and Propofol on seizure parameters and seizure quality in electroconvulsive therapy: a retrospective study. Eur. Arch. Psychiatry Clin. Neurosci. 265, 255–261. https://doi.org/10.1007/s00406-013-0420-5.

IBM Corp, 2016. IBM SPSS Statistics for Windows. IBM Corp, Armonk, NY Version 24.0.

Ingram, A., Saling, M.M., Schweitzer, I., 2008. Cognitive side effects of brief pulse electroconvulsive therapy: a review. J. ECT 24 (1), 3–9. https://doi.org/10.1097/YCT.0b013e31815ef24a.

Kellner, Ch.H., Li, D., Maron, L., 2009. Anesthesia for electroconvulsive therapy. In: Swartz, C.M. (Ed.), Electroconvulsive and Neuromodulation Therapies. Cambridge University Press, New York, pp. 412–429.

Krystal, A.D., 2010. Ictal electroencephalografic response. In: Mankad, M.V., Beyer, J.L., Weiner, R.D., Krystal, A.D. (Eds.), Clinical Manual of Electroconvulsive Therapy, first edition. American Psychiatric Publishing, Arlington, pp. 105–128.

López-Ibor, Aliño J.J., Valdés, Miyar M., 2002. DSM-IV-TR. Manual diagnóstico y estadístico de los trastornos mentales. Masson, Barcelona.

Mankad, M.V., Weiner, R.D., 2010. Anesthetics and other medications. In: Mankad, M.V., Beyer, J.L., Weiner, R.D., Krystal, A.D. (Eds.), Clinical Manual of Electroconvulsive Therapy, first ed. American Psychiatric Publishing, Arlington, pp. 81–93.

Martínez-Amorós, E., Gálvez, V., Cardoner, N., Palao, D, Bernardo, M, Urretavizcaya, M., 2015. Electroconvulsive therapy practice in Catalonia. A survey study comparing data from 1993 and 2010. J. ECT 31 (1), 43–49. https://doi.org/10.1097/YCT.0000000000000150.

Mitchell, P., Torda, Th., Hickie, I., Ch, Burke, 1991. Propofol as an anaesthetic agent for ECT: effect on outcome and length of course. Aust. N. Z. J. Psychiatry 25, 255–261. https://doi.org/10.3109/00048679109077742.

Petrides, G., Braga, R.J., Fink, M., Mueller, M, Knapp, R, Husain, M., 2009. Seizure threshold in a large sample: implications for stimulus dosing strategies in bilateral electroconvulsive therapy. A Report from CORE. J. ECT 25 (4), 232–237.

Rattehalli, R.D., Thirthalli, J, Rawat, V., Gangadhar, B.N., Adams, C.E., 2009. Measuring electroencephalographic seizure adequacy during electroconvulsive therapy. A comparison of 2 definitions. J. ECT 25 (4), 243–245. https://doi.org/10.1097/YCT.0b013e3181a09d4d.

Scott, A.I.F., Waite, J., 2013. Monitoring a course of ECT. In: Waite, J., Easton, A. (Eds.), The ECT Handbook, third ed. The Royal College of Psychiatrists, Glasgow, pp. 60–70.

Simpson, K.H., Halsall, C.M.E., Stewart, K.G., 1988. Propofol reduces seizure duration in patients having anaesthesia for electroconvulsive therapy. Br. J. Anaesth. 61, 343–344.

Singh, P.M., Arora, S., Borle, A., Varma, P., Trikha, A., Goudra, B.G., 2015. Evaluation of etomidate for seizure duration in electroconvulsive therapy: a systematic review and meta-analysis. J. ECT 31 (4), 213–225. https://doi.org/10.1097/YCT.0000000000000212.

Swartz, C.M., 2009. Heart rate and electroconvulsive therapy. In: Swartz, C.M. (Ed.), Electroconvulsive and Neuromodulation Therapies. Cambridge University Press, New York, pp. 477–484.

Vaidya, P.V., Anderson, E.L., Bobb, A., Pulia, K., Jarayam, G., Reti, I., 2012. A within-subject comparison of Propofol and methohexital anesthesia for electroconvulsive

therapy. J. ECT 28 (1), 14–19. https://doi.org/10.1097/YCT.0b013e31823a4220.
van Waarde, J.A., Muller, M.E.M.T, Verwey, B., van der Mast, R.C., 2009 (a) (a). Exceptionally high initial seizure threshold in a catatonic patient treated with electroconvulsive therapy. J. ECT 25 (2), 121–124. https://doi.org/10.1097/YCT.0b013e31817c73c3.
van Waarde, J.A, Verwey, B., van der Mast, R., 2009 (b) (b). Meta-analysis of initial seizure thresholds in electroconvulsive therapy. Eur. Arch. Psychiatry Clin. Neurosci. 259, 467–474. https://doi.org/10.1007/s00406-009-0011-7.
Vaughn McCall, W., 2009. Stimulus dosing. In: Swartz, C.M. (Ed.), Electroconvulsive and Neuromodulation Therapies. Cambridge University Press, New York, pp. 447–467.
Wang, N., Wang, X.H., Lu, J., Zhang, J.Y., 2011. The effect of repeated etomidate anesthesia on adrenocortical function during a course of electroconvulsive therapy. J. ECT 27 (4), 281–285. https://doi.org/10.1097/YCT.0b013e3182182be0.
Weiner, R.D., 2010. Clinical Applications. In: Mankad, M.V., Beyer, J.L., Weiner, R.D., Krystal, A.D. (Eds.), Clinical Manual of Electroconvulsive Therapy, first ed. American Psychiatric Publishing, Arlington, pp. 59–79.