Ictal Quality Parameters in ECT

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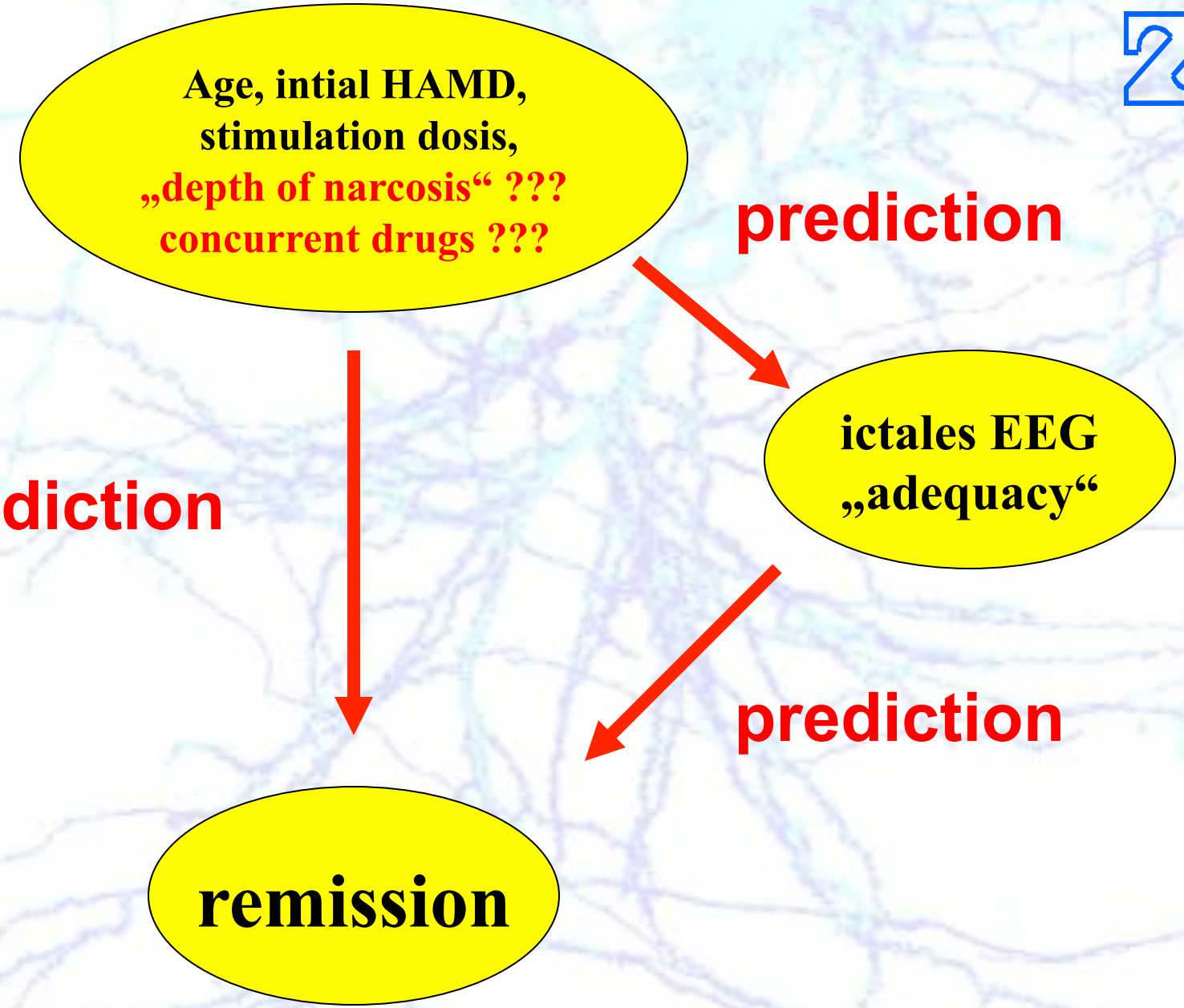

Age, intial HAMD,
stimulation dosis,
„depth of narcosis“ ???
concurrent drugs ???
prediction
ictales EEG
„adequacy“
prediction
prediction
remission

ECT – anesthesia:

- thiopental	3-5 mg/kg
- methohexital	50-120 mg
- etomidate	0.15-0.3 mg/kg
- propofol	1-2 mg/kg

German guidelines for tx of status epilepticus

=>	lorazepam	up to 10mg i.v.
=>	phenytoin	up to 30 mg/kg KG i.v.
=>	phenobarbital	20 mg/kg KG i.v.
=>	thiopental	**4-7 mg/kg** KG i.v.
vs.	propofol	**1-2 mg/kg** KG i.v.
vs.	midazolam or valproate	

Dosing of ECT anesthetics

- experience of the anesthesiologist

- experience of previos ECT sessions
  - time needed for full recovery
  - patient remembers muscle relaxation
  - systematic / non-systematic movements of the “cuffed” limb

- objective criteria for

“dosing” and “timing”

do not exist …

Bispectral Index Monitoring (BIS)

- has been developed to prevent intraoperative awareness

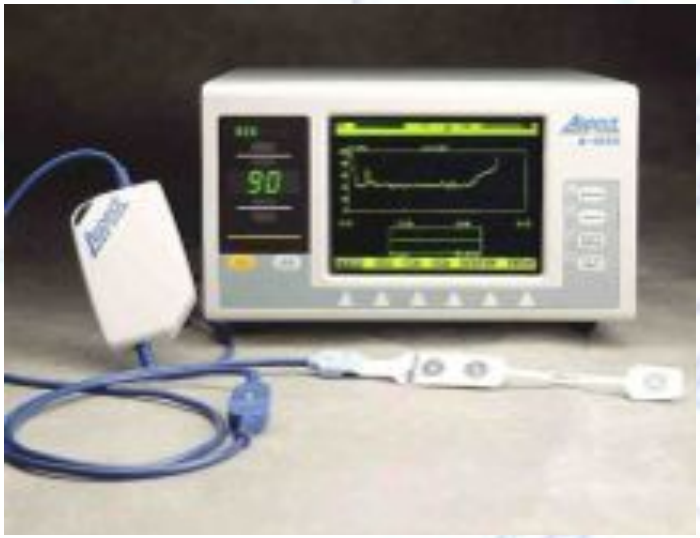
- uses combined EEG/EMG to derive a measure for "cortical integrity" inter alia by analyzing coherences between different frequency bands

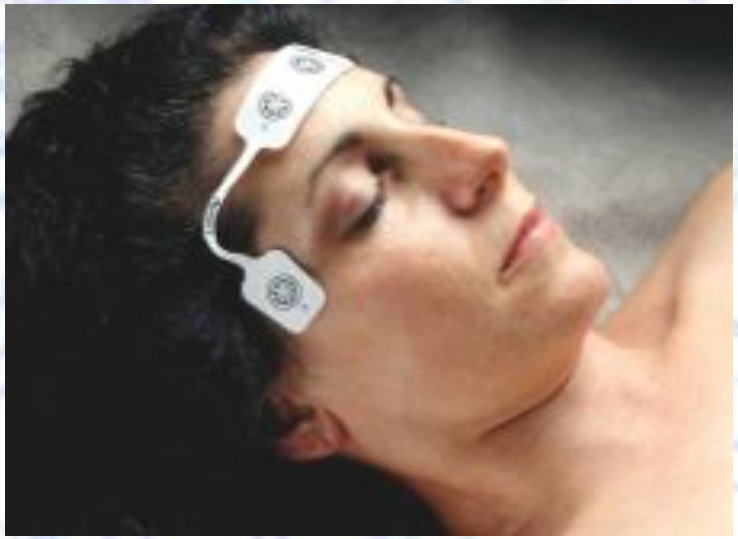
- More precisely: bispectrum is a 3rd order Fourier transformation that includes amplitude, phase AND coherence information. BIS is a normalized index function of the bispectrum.

0	-	electrically silent brain
100	-	fully vigilant patient

Bispectral Index Monitoring (BIS)

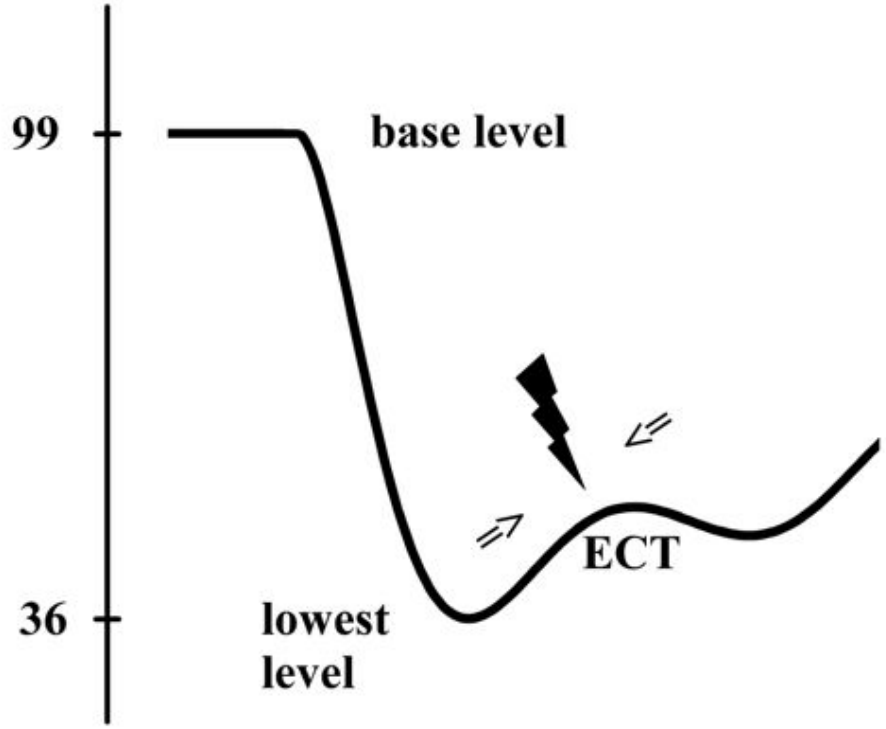
- BIS more **valid** regarding “hypnosis” compared with other algorithms like spectral edge frequency (SEF), median frequency (MF), or delta, theta, alpha, beta power





Liu J, Singh H, White PF (1996) Anesthesiology 84:64-69
Schmidt GN, Bischoff P, et al. (2005) Anaesthesia 60:228-234

Does BIS correlate with thiopental dosis ?



Lowest level: **YES !**
n= 48, p = 0.04, r = 0.29

Later: **No !**

A. Sartorius et al., Br J Anaesth. 2006.
A. Sartorius et al., Pharmacopsychiatry. 2006.

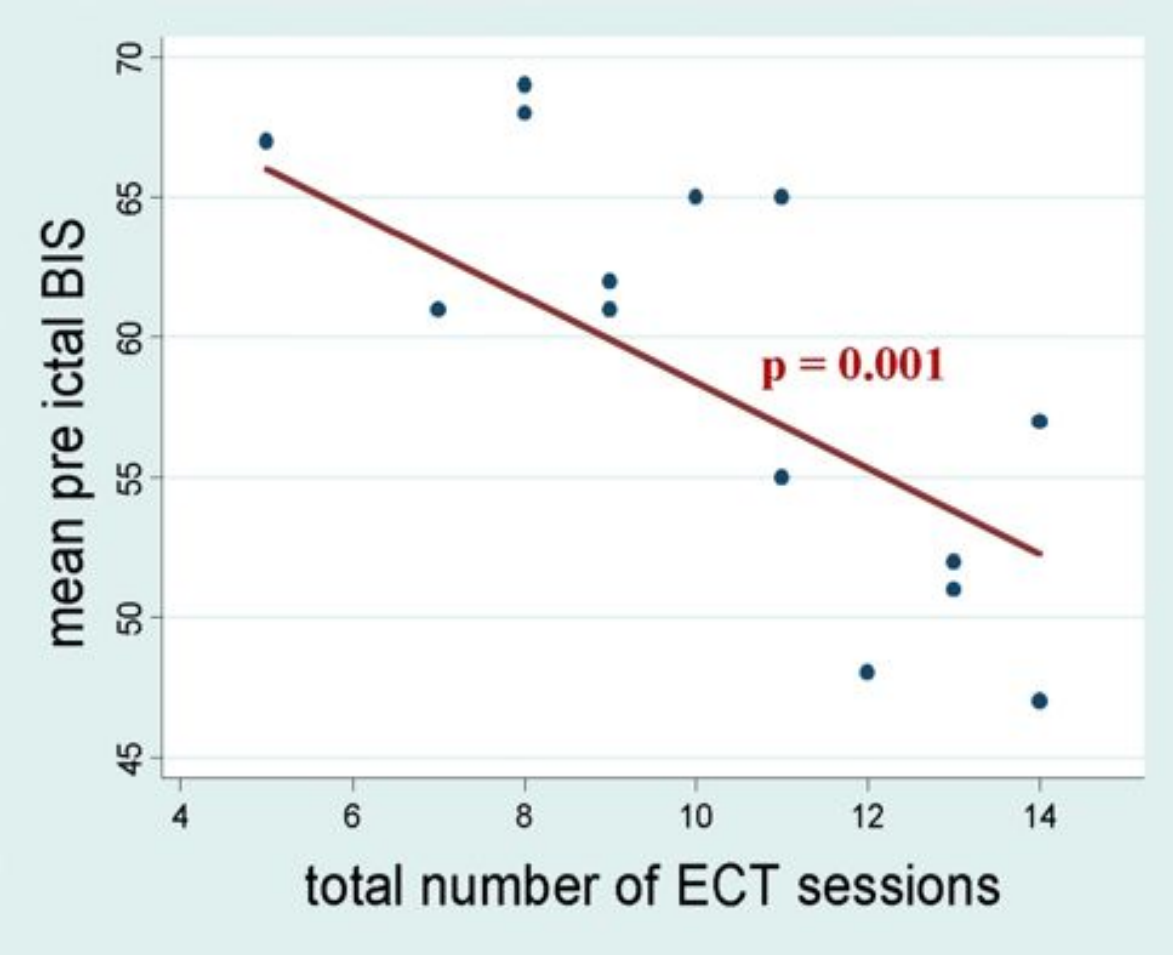
CIMH first study on depth of anesthesia

- 22 MDE patients
- 51 ±14 y
- 64 % remitter, 23% responder

- initial $HAMD_{21}$ = 27.7 ± 9
- final $HAMD_{21}$ = 8.5 ± 5

- number of ECT sessions = 10 ± 3 (min 5, max 14)
- mean applied “energy” = 40 ± 20 %

CIMH first study on depth of anesthesia



A. Sartorius et al., ECT anesthesia: the lighter the better? Pharmacopsychiatry. 2006 Nov;39(6):201-4.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL THERAPEUTICS

Electroconvulsive Therapy for Depression

Sarah H. Lisanby, M.D.

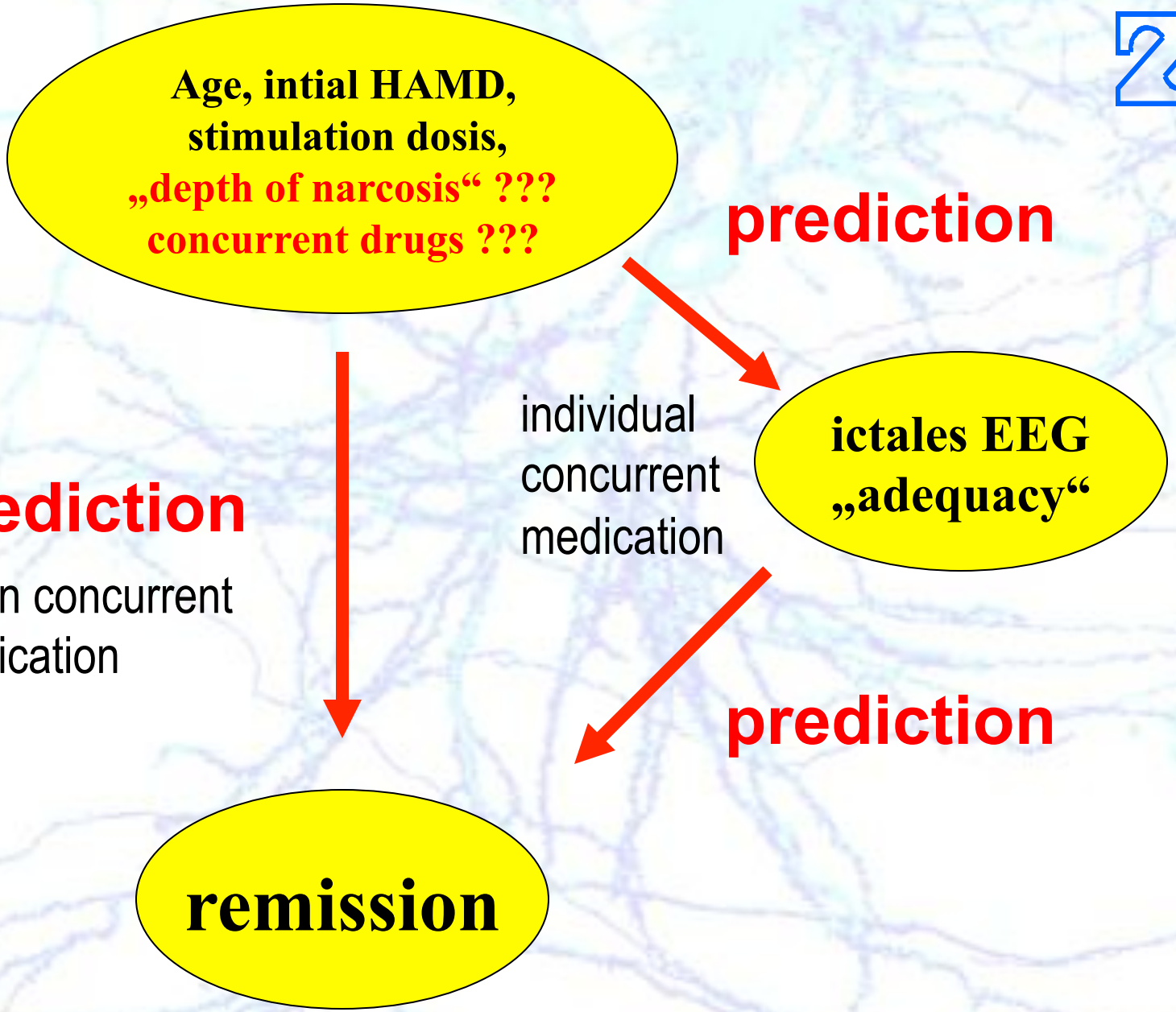
N ENGL J MED 357;19 WWW.NEJM.ORG NOVEMBER 8, 2007

Correspondence:

1. Dettling / Anghelescu / Bajbouj
2. Guevara-Cuellar / Pineda-Cañar

Reply of S. Lisanby:

Sartorius et al.:
“concomitant medications were not controlled”


Age, intial HAMD,
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mean concurrent
medication
prediction
remission

CIMH second study on depth of anesthesia

- 41 patients with MDE (totalling in 411 ECTs)

- 99 different drugs in 24h time window before individual ECT

- 25 of those have been either
  - benzodiazepines
  - antidepressants or
  - antipsychotics

Bundy BD, Hewer W, Andres FJ, Gass P, Sartorius A.
J Clin Psychiatry. 2010 Jun;71(6):775-7.

CIMH second study on depth of anesthesia

Table 3: Mean equivalence doses

	mean of all ECT sessions					mean of substance positive ECT sessions		
	last 24 h / bw		last 24 h			last 24 h		
equivalent of	mean	sd	mean	sd	n	mean	sd	n
diazepam (mg)	0.13	0.15	8.3	9.7	411	**11.3**	9.7	300
amitriptyline (mg)	0.80	1.3	58	101	411	**166**	106	144
chlorpromazine (mg)	0.63	1.9	49	158	411	**274**	283	73

Bundy BD, Hewer W, Andres FJ, Gass P, Sartorius A.
J Clin Psychiatry. 2010 Jun;71(6):775-7.

CIMH second study on depth of anesthesia

Table 2: Patient characteristics

	remitter (n=19)		responder (n=12)		non-responder (n=10)		anova p	all (n=41)	
	mean	sd	mean	sd	mean	sd		mean	sd
age (y)	56	15	51	18	60	16	0.39	55	16
body weight (kg)	67	12	71	15	67	22	0.73	68	16
initial HAMD	26	7	31	5	25	6	0.05	27	6
final HAMD	5	2	12	2	17	4	<0.0001	10	6
thiopental (mg/kg bw)*	4.1	1.8	4.3	1.0	3.6	0.9	0.47	4.0	1.4
total # of ECTs	10	4	10	4	10	3	0.99	10	4
at first ECT treatment:									
stimulation energy (%)	21	23	15	7	20	16	0.69	19	18
diazepam equivalent (mg/d)	7.6	6.1	13	11	8.8	7.8	0.22	9.6	8.4
amitriptyline equivalent (mg/d)	74	107	85	150	103	128	0.84	84	123
chlorpromazine equivalent (mg/d)	32	69	83	218	259	456	0.08	102	266

Response was defined as an Hamilton Depression Scale ($HAMD_{21}$) reduction of at least 50% compared to the value at onset. Remission was defined as a final $HAMD_{21} \leq 8$. Initial HAMD scores were taken before first ECT session, final HAMD scores during the week after the last ECT session.

Bundy BD, Hewer W, Andres FJ, Gass P, Sartorius A. J Clin Psychiatry. 2010 Jun;71(6):775-7.

CIMH second study on depth of anesthesia

some established markers of “seizure adequacy”:

- seizure concordance
- postictal suppression index
- seizure energy index
- motor response time
- duration of EEG seizure activity
- peak heart rate
- midictal amplitude
- total seizure coherence

ictal markers of “seizure adequacy” are not independent from each other:

- seizure concordance
- postictal suppression index
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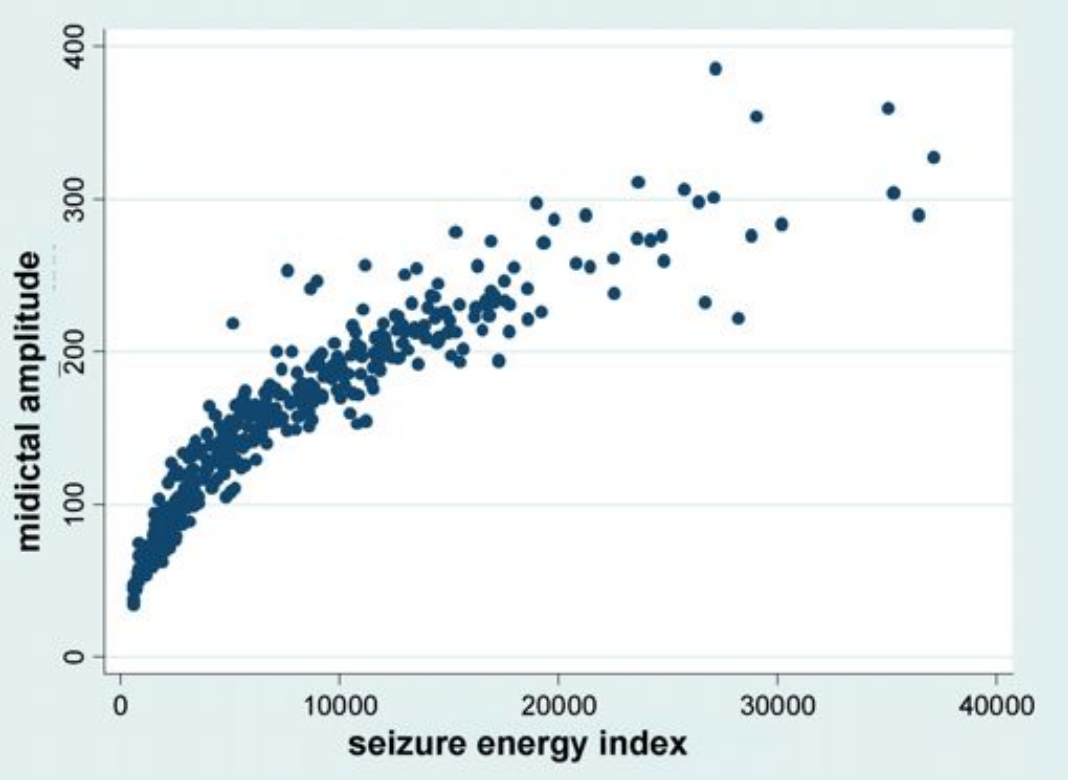
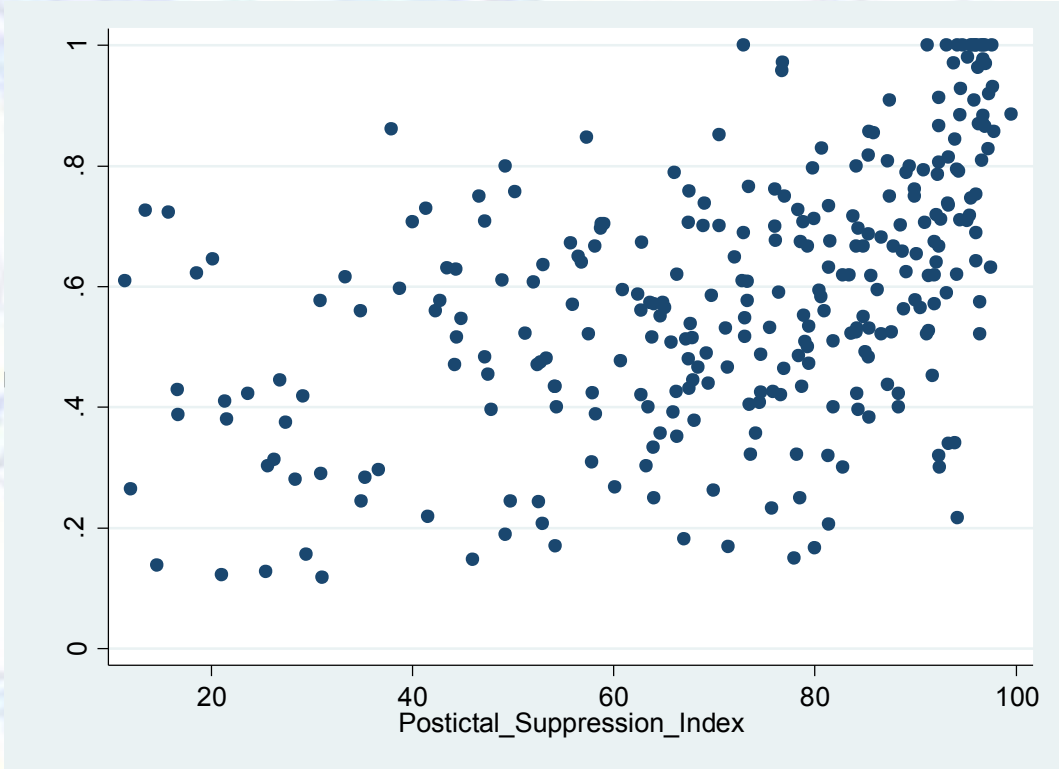


ictal markers of “seizure adequacy” are not independent from each other:

- seizure concordance = motor response time / duration of EEG seizure activity
- postictal suppression index
- seizure energy index
- motor response time
- duration of EEG seizure activity
- peak heart rate
- midictal amplitude
- total seizure coherence



ictal markers of “seizure adequacy”:

We identified 5 possibly independent groups:

1. duration:
    - EEG determined seizure duration
    - motor response time

2. amplitude:
    - midictal amplitude
    - seizure energy index

3. central inhibition:
    - post-ictal suppression index
    - seizure concordance

4. coherence:
    - seizure coherence

5. sympathetic activation:
    - maximal post-stimulation heart rate

Table 1: Influence of concurrent drugs on seizure adequacy

		independent variables															
		energy		BIS		age		HAMD$_i$		thiopental		benzo-diazepines		AP		AD	
dependent variables:	r^2	cc	p	cc	p	cc	p	cc	p	cc	p	cc	p	cc	p	cc	p
EEG seizure duration	0.19	-.17	**0.001**	.22	**0.001**	-.18	0.13	.29	0.33	-.78	0.58	-.20	0.12	.00	0.72	-.02	0.08
motor response time	0.43	-.17	**0.001**	.21	**0.001**	-.25	**0.002**	.41	***0.03***	-.41	0.66	-.08	0.34	.00	0.61	-.00	0.94
midictal amplitude	0.26	-.29	***0.05***	.26	0.32	-2.02	**0.001**	.73	0.46	1.68	0.75	.15	0.76	-.02	0.41	-.01	0.89
seizure energy index	0.26	1.25	0.92	.41	***0.04***	-216	**0.001**	121	0.29	697	0.16	20	0.64	-.63	0.83	-2.8	0.45
postictal suppression	0.14	-.12	***0.03***	.23	***0.01***	-.21	0.11	-.11	0.72	.11	0.95	.28	0.09	.01	0.55	-.01	0.57
concordance	0.33	-.002	**0.001**	.002	**0.001**	-.003	**0.004**	.004	0.07	.00	0.97	-.00	0.36	.00	0.68	.0002	***0.03***
ictal coherence	0.14	-.08	***0.05***	.18	***0.02***	-.36	**0.004**	-.09	0.77	2.64	0.09	.02	0.90	.01	0.26	-.02	0.14
maximal heart rate	0.20	-.02	0.67	.22	***0.008***	-.68	**0.001**	.28	0.45	-2.5	0.15	-.20	0.21	-.01	0.20	-.01	0.48

The multivariate repeated measurement regression analysis was separately computed for every dependent variable including all independent variables. All dependent variables were quantified by the Thymatron ECT device.
Significant results are shown in ***bold italic*** letters, results, which are statistically significant after correction for multiple testing are shown in **underlined bold** letters. Bonferroni correction was set at $\alpha = 0.05/8 = 0.00625$. Concordance is the ratio of motor response time and EEG seizure duration and a marker of the central inhibition power.
cc = correlation coefficient, r^2 = explained variance
energy = ECT stimulation energy, BIS = depth of induced narcosis (quantified as bispectral index or BIS)
HAMDi = initial severeness of depressive episode (quantified as Hamilton depression 21 item scale)

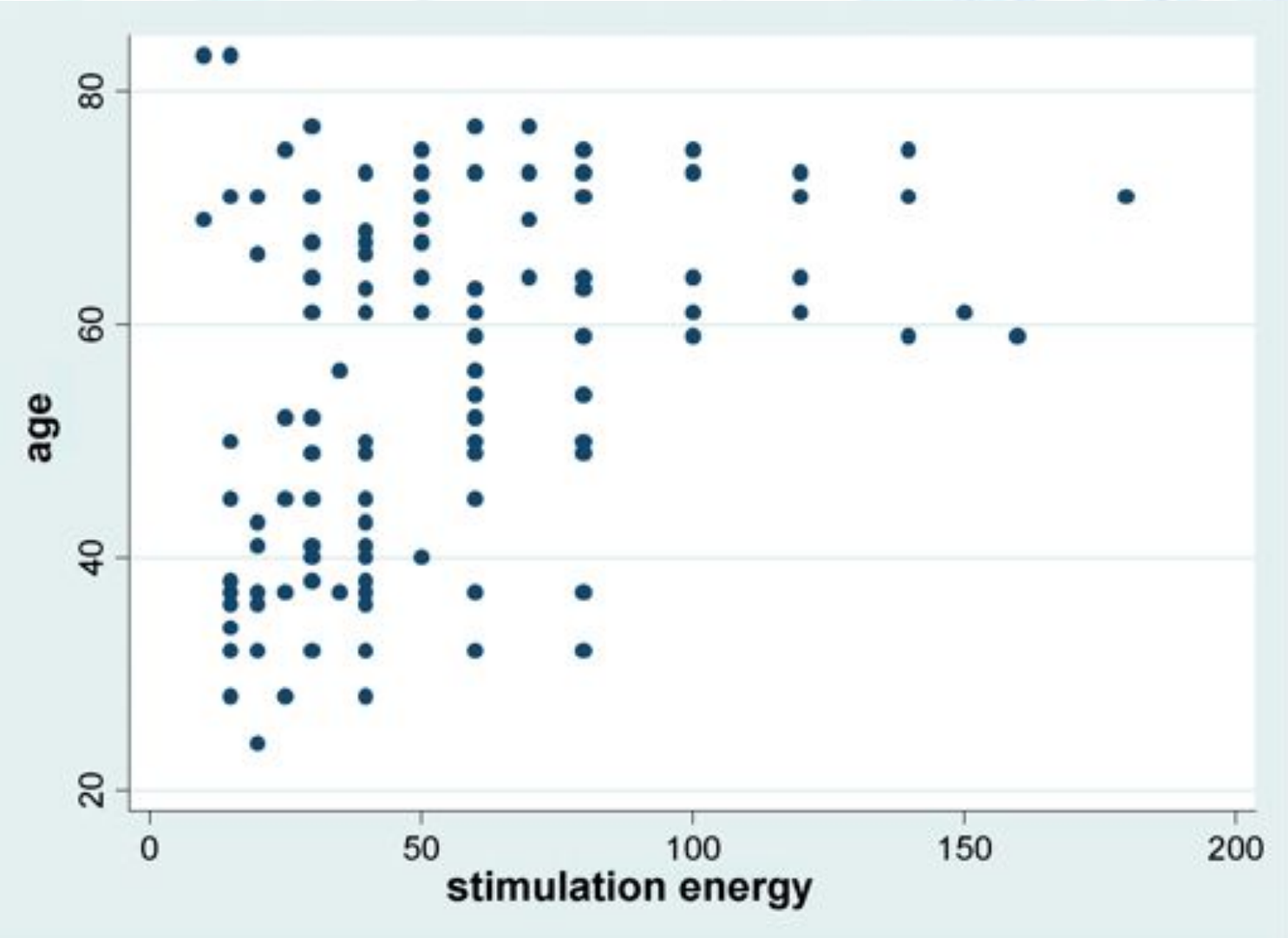
Bundy BD, Hewer W, Andres FJ, Gass P, Sartorius A.
J Clin Psychiatry. 2010 Jun;71(6):775-7.

Conclusion:

concurrent psychotropic medications at typical doses do not interfere with ECT

- at least at a level of ictal parameters predictive for ECT response

Some replications of old findings:



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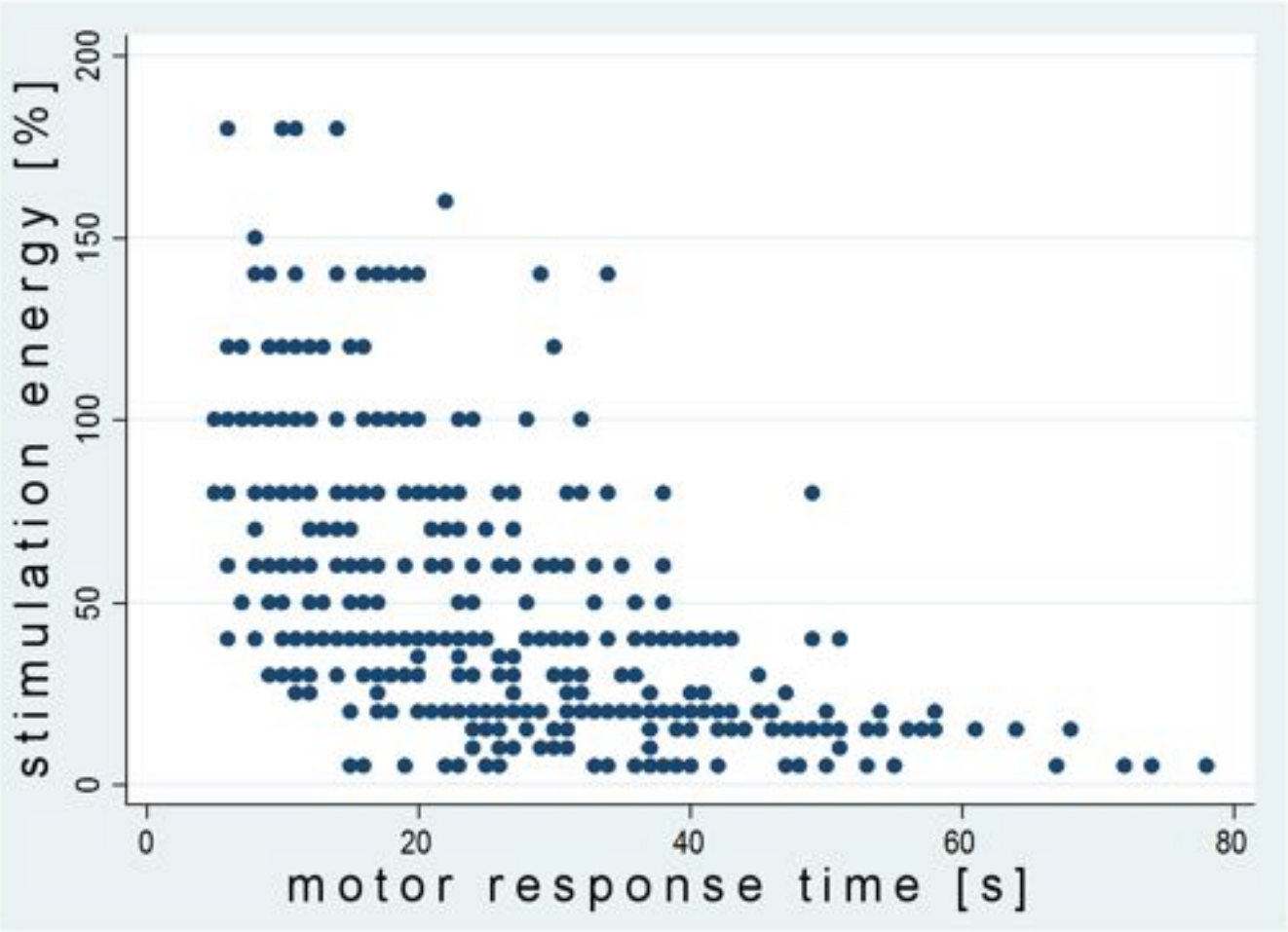
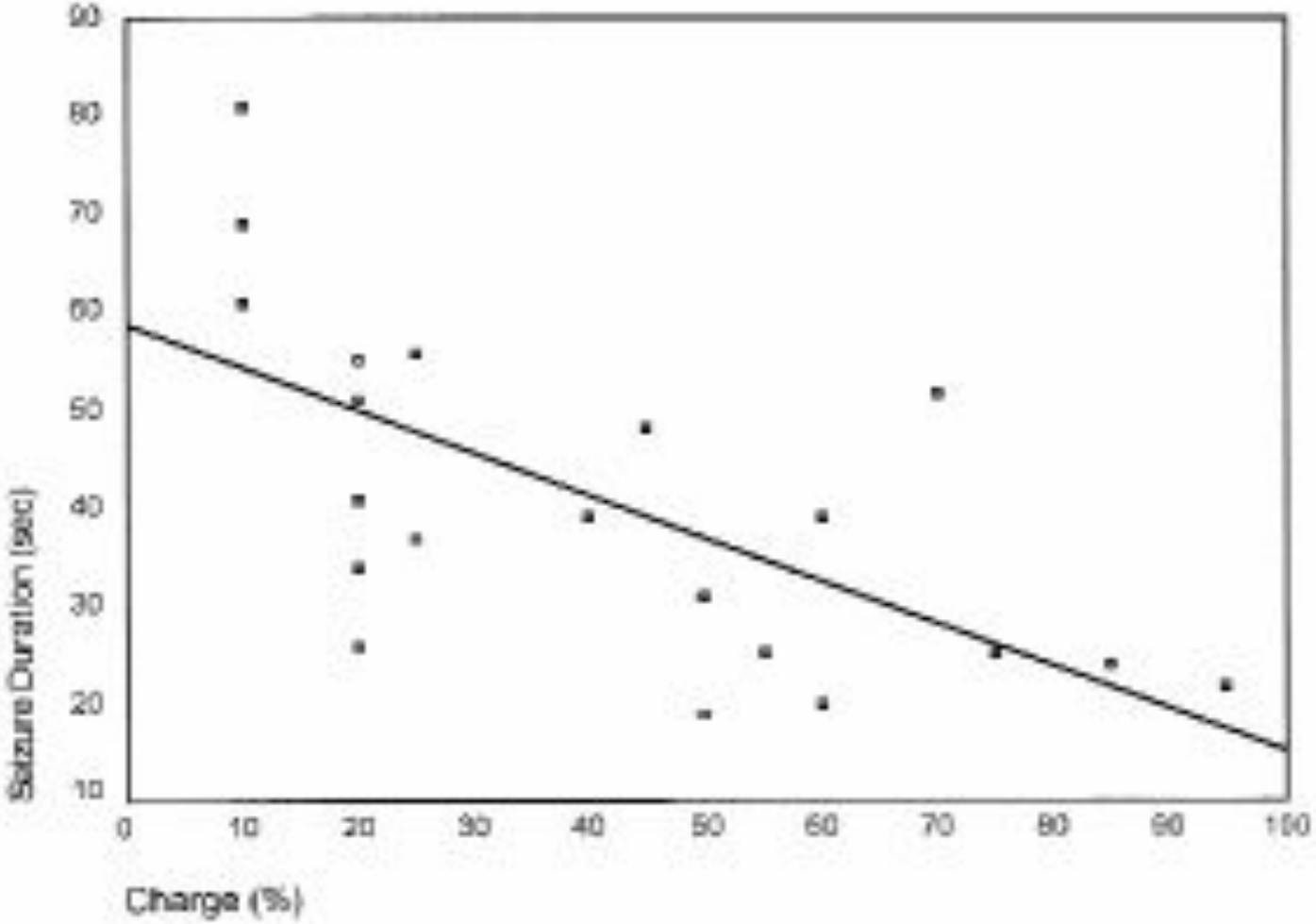
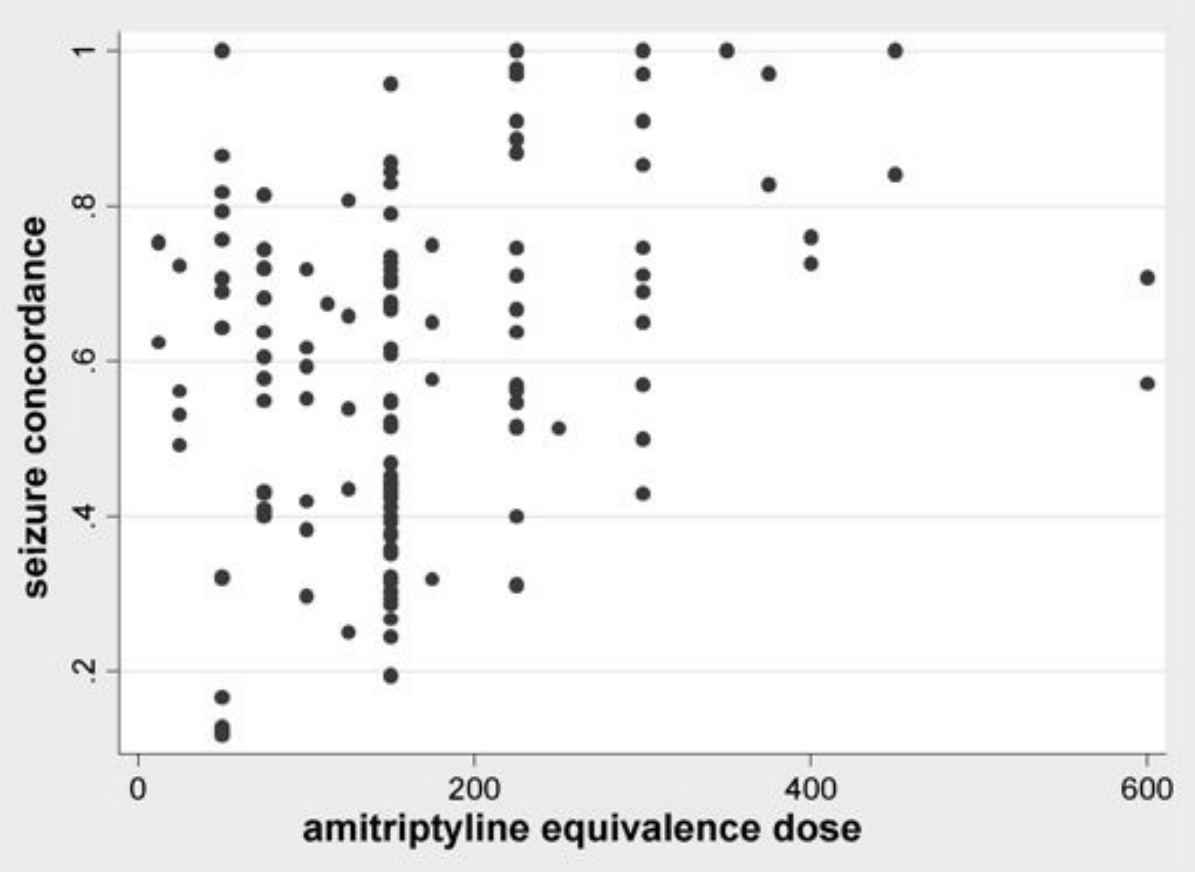


$r^2 = 0.32$



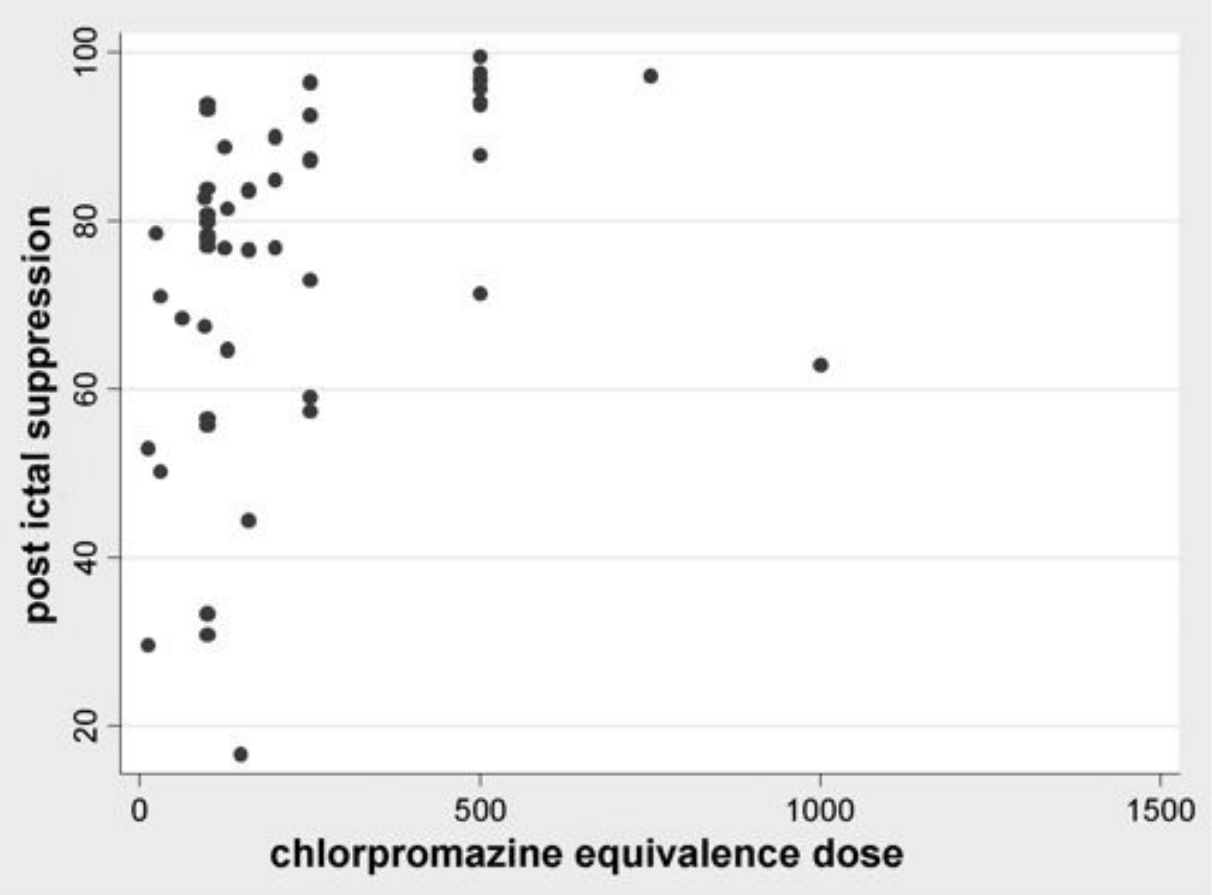
Frey R, Heiden A, Scharfetter J, Schreinzer D, Blasbichler T, Tauscher J, Felleiter P, Kasper S.
J ECT. 2001 Jun;17(2):102-8.

Concordance and antidepressive medication



Seizure concordance and equivalence dosage of amitriptyline [mg / 24h] correlates positively (Pearson: $t = 4.02$, $p < 0.001$, $r^2 = 0.10$, $n = 141$).
In other words: Higher doses of antidepressants led to a better central inhibition of a seizure predicting better outcome.

Post-ictal suppression and antipsychotics



Analyzing post hoc only patients who received antipsychotics led to a significant correlation of postictal suppression and chlorpromazine equivalent dosis (Pearson: $r^2 = 0.18$, $t = 3.25$, $p = 0.002$).

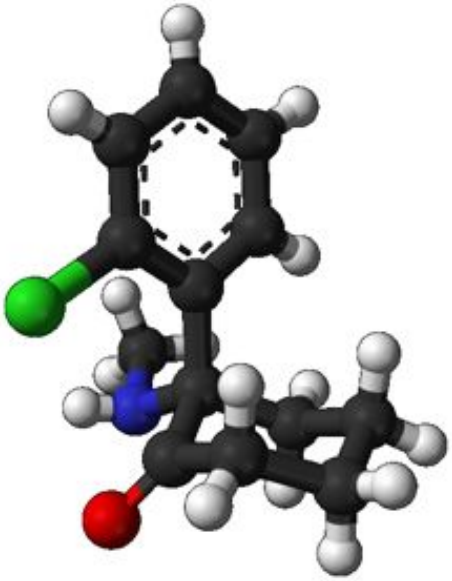
Back to anesthetics:

If BIS - or “light” anesthesia
- or better less anticonvulsive action
resulting from anesthetics is important

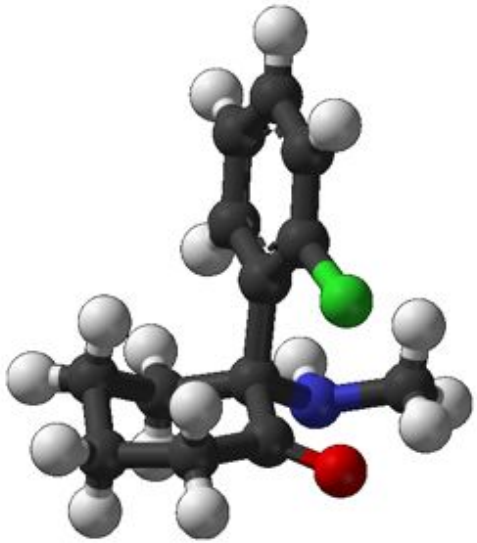
Why we don’t use an anesthetic without anticonvulsive properties ?

A. Sartorius[1]
E. M. Muñoz-Canales[1]
B. Krumm[2]
A. Krier[3,4]
F. J. Andres[4]
H.-J. Bender[4]
F. A. Henn[1]

ECT Anesthesia: The Lighter the Better?




Kellogg's
Special
K



ECT and ketamine

pros:

1. Ketamine probably posseses a unique intrinsic antidepressive potential

2. Ketamine has no anticonvulsive action

3. Ketamine may posses neuroprotective properties as an NMDA-antagonist

4. Ketamine is comparable with amantadine and memantine,
   which are used as 2nd / 3rd line therapy in catatonia.

cons:

1. Ketamine acts non-depressively on the cardio-vascular systeme (like e.g. barbiturates)

2. Ketamine dose-dependently induces psychiatric side-effects
   (basically derealisation and depersonalisation, which can lead to anxiety)

ORIGINAL ARTICLE

A Randomized Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression

Carlos A. Zarate, Jr, MD; Jaskaran B. Singh, MD; Paul J. Carlson, MD; Nancy E. Brutsche, MSN; Rezvan Ameli, PhD; David A. Luckenbaugh, MA; Dennis S. Charney, MD; Husseini K. Manji, MD, FRCPC

Arch Gen Psychiatry 2006

ORIGINAL ARTICLE

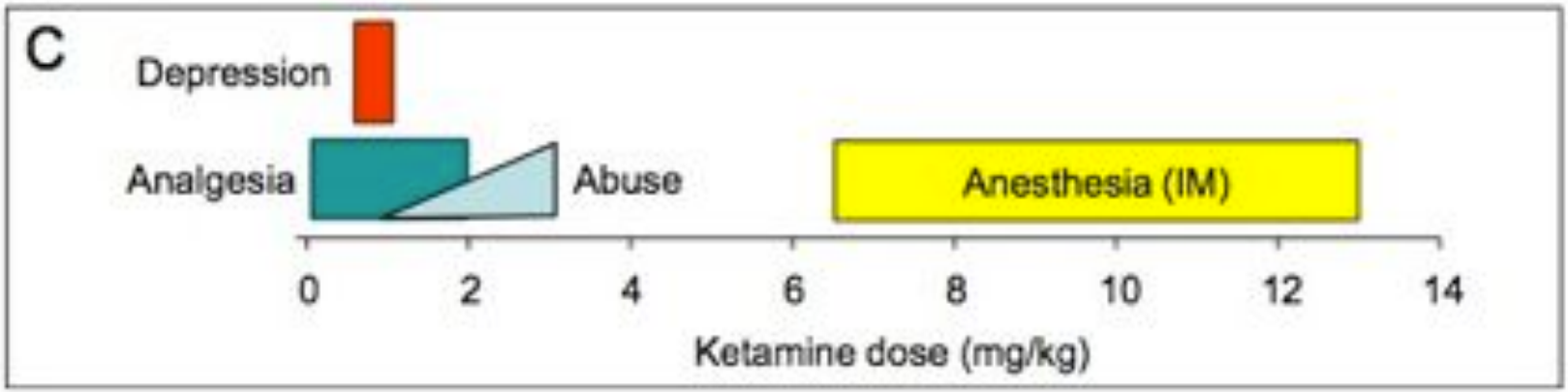
A Randomized Add-on Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Bipolar Depression

Nancy Diazgranados, MD, MS; Lobna Ibrahim, MD; Nancy E. Brutsche, MSN; Andrew Newberg, MD; Phillip Kronstein, MD; Sami Khalife, MD; William A. Kammerer, MD; Zenaide Quezado, MD; David A. Luckenbaugh, MA; Giacomo Salvadore, MD; Rodrigo Machado-Vieira, MD, PhD; Husseini K. Manji, MD, FRCPC; Carlos A. Zarate Jr, MD

Arch Gen Psychiatry 2010

ketamine racemate 0.5 mg/kg bw i.v. over 40 mins

dose-effect relation



Glue et al., Biol Psychiatry, 2011

ketamine racemate in mg/kg bw i.m. as bolus

Eur Arch Psychiatry Clin Neurosci
DOI 10.1007/s00406-011-0205-7

ORIGINAL PAPER

Clinically favourable effects of ketamine as an anaesthetic for electroconvulsive therapy: a retrospective study

Laura Kranaster · Jutta Kammerer-Ciernioch · Carolin Hoyer · Alexander Sartorius

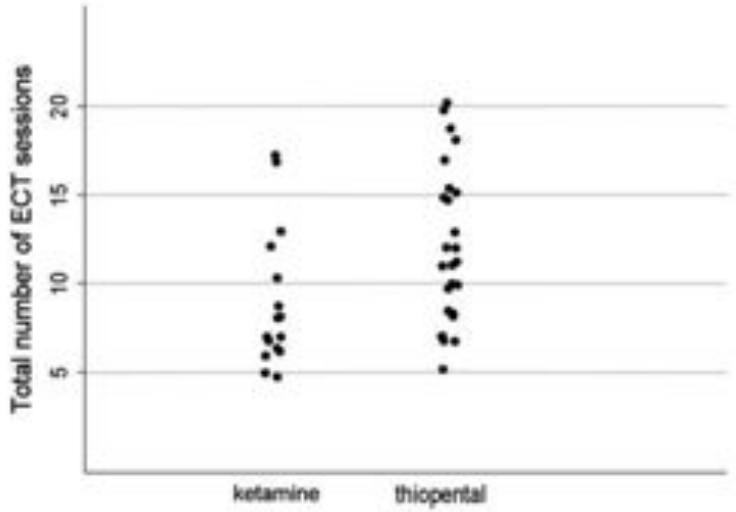


Fig. 1 Total number of ECT sessions of each individual patient in the ketamine (8.9, SD: 3.9) and thiopental (11.9, SD: 4.4) group ($P = 0.015$, one sided) point towards a better antidepressant effectiveness of ketamine

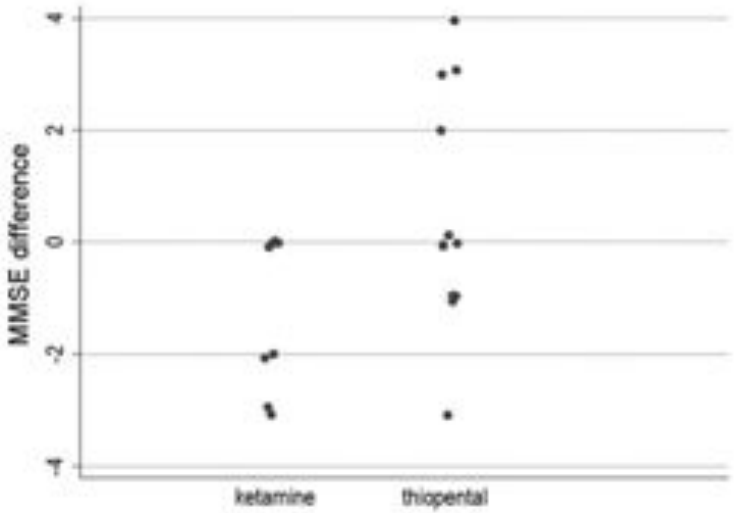


Fig. 3 Differences of the MMSE score before and after ECT of each individual patient in the ketamine (1.2, SD: 1.3, $N = 9$) and thiopental (−0.5, SD: 2.1, $N = 12$) group ($P = 0.025$, one sided) demonstrate a better cognitive outcome after ECT in the ketamine group

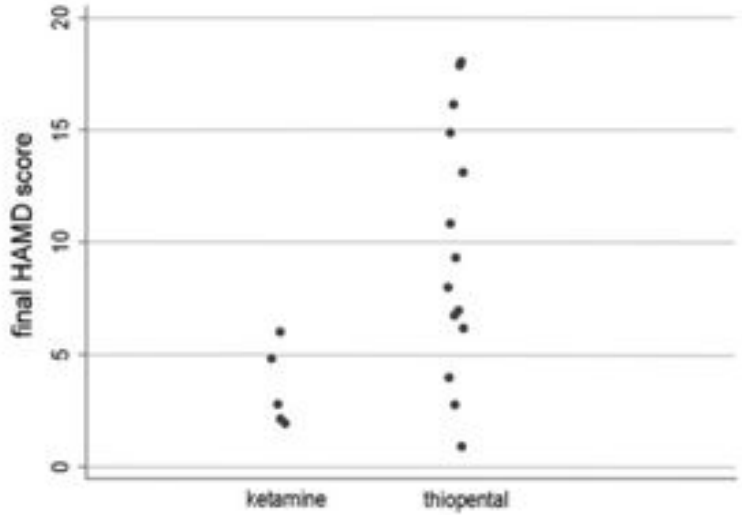


Fig. 2 Final HAM-D_{21} score after ECT of each individual patient in the ketamine (3.6, SD: 1.8, $N = 5$) and thiopental (9.7, SD: 5.6, $N = 14$) group ($P = 0.015$, one sided) indicate a better antidepressant response in the ketamine group

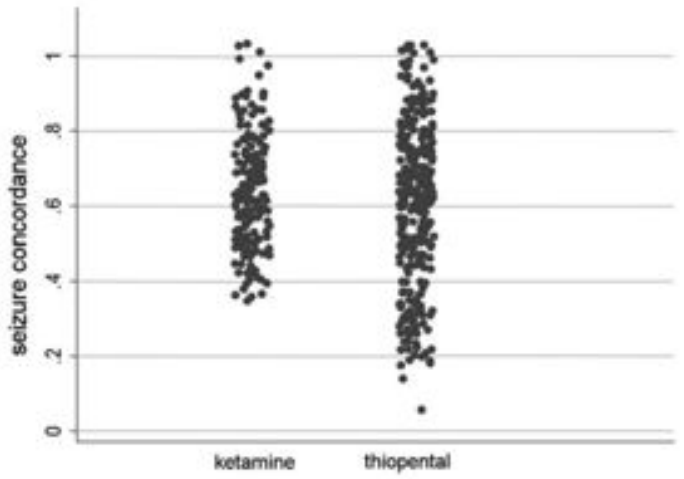


Fig. 5 Individual concordance (ratio of motor response time over EEG seizure duration) of each seizure in the ketamine (0.64, SD: 0.15, $N = 174$) and thiopental (0.61, SD: 0.21, $N = 315$) group ($P = 0.045$, one sided). Ketamine enhances the concordance and thus seizure quality

Table 3 Seizure data of both groups

	Ketamine	Thiopental	*P* (one sided)
N total	176	321	–
S-ketamine (mg)	46.7 ($N = 173$) (SD 12.0)	–	–
Thiopental (mg)	–	236.0 ($N = 320$) (SD 64.3)	–
Stimulation dose (%)	36.9 ($N = 175$) (SD 28.6)	39.5 ($N = 320$) (SD 27.9)	NS
Unilateral stimulation (%)	73 ($N = 175$) (SD 45)	82 (SD 39)	NS (0.7139)
Seizure duration (motor) (s)	31.1 ($N = 175$) (SD 23.6)	29.8 ($N = 315$) (SD 14.1)	NS
Seizure duration (EEG) (s)	49.5 ($N = 174$) (SD 17.7)	50.2 ($N = 317$) (SD 22.8)	NS
Concordance	0.64 ($N = 174$) (SD 0.15)	0.61 ($N = 315$) (SD 0.21)	0.045
Urapidil (mg)	9.5 (SD 13.1)	6.9 (SD 10.5)	0.030

Presented as means with standard deviation (SD)

NS not significant

Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update

Steven M. Green, MD, Mark G. Roback, MD, Robert M. Kennedy, MD, Baruch Krauss, MD, EdM

From the Department of Emergency Medicine, Loma Linda University Medical Center and Children's Hospital, Loma Linda, CA (Green); the Department of Pediatrics, University of Minnesota, Minneapolis, MN (Roback); the Division of Emergency Medicine, St. Louis Children's Hospital, Washington University, St. Louis, MO (Kennedy); and the Division of Emergency Medicine, Children's Hospital Boston and Department of Pediatrics, Harvard Medical School, Boston, MA (Krauss).

Contraindications: Absolute (Risks Essentially Always Outweigh Benefits)

- Age younger than 3 months (higher risk of airway complications)
- Known or suspected schizophrenia, even if currently stable or controlled with medications (can exacerbate condition)

Preliminary evaluation of clinical outcome and safety of ketamine as an anesthetic for electroconvulsive therapy in schizophrenia.
Kranaster L, Hoyer C, Janke C, Sartorius A.
World J Biol Psychiatry. 2012 Mar 8. [Epub ahead of print]

Case	#1	#2	#3	#4	#5	#6
Type	paranoid	catatonia	paranoid	paranoid	paranoid	paranoid
Sex	male	male	female	male	female	male
Age	53	25	65	26	47	57
No. ECT	34	52*	31	15	11	5
BMI	?	19	22	?	20	27
Duration of Illness (in years)	38?	?5.5	34	0.5?	1.0?	14?
Psychotrophic medication during ECT treatment	Haloperidol, Lorazepam	Clozapine, Risperidone, Lorazepam, Escitalopram	Olanzapine, Venlafaxine	Risperidone, Lorazepam	Aripiprazole	Olanzapine, Amisulpride, Mirtazapine
Outcome	Remission	Response	No response	Remission	Response	Remission

Table 1: The demographic data of the patients with schizophrenia, who received ketamine as narcotic for ECT. (*including maintenance ECT)

Conclusions:

1. It ‘s worth controlling for depth of anesthesia (BIS-monitoring)

2. It ‘s worth looking for ictal parameters (predicting session adequacy)

3. It ‘s worth keeping alternatives in mind (ketamine)

4. It ‘s probably not worth to limit concurrent drugs
   (at least at typical doses and due to ictal parameters)

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