



Zentralinstitut
für Seelische
Gesundheit

Does Ketamine Improve ECT?

NACT, Riga 23.05.2024

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Central Institute of Mental Health (CIMH)



COI – none, but:



Ketamine and ECT:



plus

ECT



story of this talk ...



alternating with

ECT



might act a little faster ...



versus

ECT

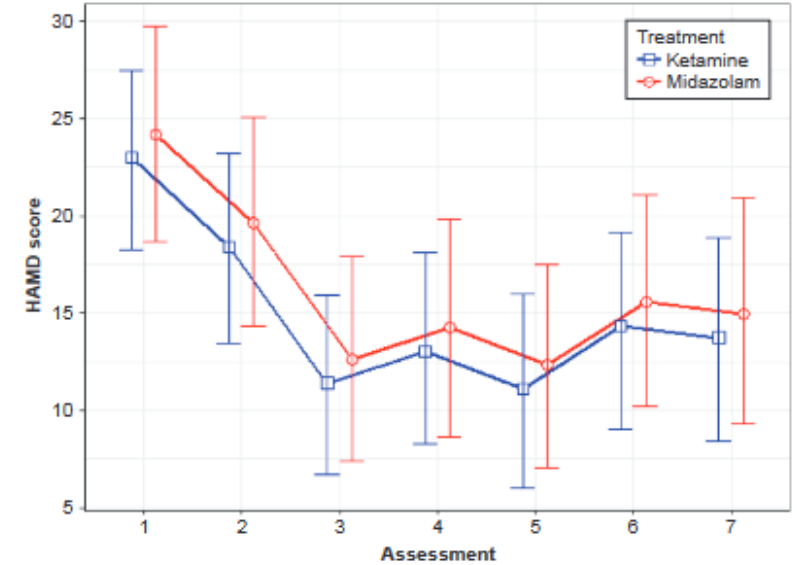


Pouya ! (next talk)

Ketamine and ECT:



alternating with **ECT**



In the first series, we performed a total of 20 ECT sessions (7 unilateral, 13 bilateral). Several key symptoms of depression failed to improve during ECT series. One week after discontinuation of ECT, the symptoms worsened (MADRS score, 46).

As a next step in our treatment algorithm, we commenced off-label intravenous esketamine treatment dosed at 0.5 mg/kg, which was increased to 0.75 mg/kg after 3 weeks because of insufficient effectiveness. Initially, 9 esketamine infusions were administered. Only a slight improvement of mood and inner restlessness occurred. At the end of the first esketamine series, the MADRS score was 36.

Because only insufficient response with ECT as well as with intravenous esketamine was achieved, a treatment algorithm of a combination of ECT and esketamine infusions on non-ECT days was considered. After a total of 6 bilateral ECT sessions (3 ECTs per week) and 4 esketamine infusions dosed at 1 mg/kg applied on non-ECT days, the patient showed rapid and significant clinical improvement. During the second week of combination treatment, lithium was discontinued because of mild disorientation, which subsided quickly after discontinuation of lithium. Otherwise, the combination treatment of ECT and esketamine was tolerated well without any relevant complications.

The combination treatment of ECT and esketamine resulted in a reduction of the MADRS score from 36 to 9 within 18 days. Less than 3 weeks after the beginning of the combination treatment, the patient was discharged from hospital. For relapse prevention, we began lithium maintenance at the previous dose and level and continued with the medication as commenced before the combination treatment of ECT and esketamine.

Per HAMD scores, 3 of the 7 ECT + ketamine subjects (42%) showed early response and remission and maintained euthymia for 3 additional visits, where one ECT +midazolam patient showed early response but this effect was not sustained, therefore none of the ECT + midazolam subjects (0%) achieved early remission .

Kavakbasi E, Hassan A, Baune BT. Combination of Electroconvulsive Therapy Alternating With Intravenous Esketamine Can Lead to Rapid Remission of Treatment Resistant Depression. J ECT. 2021 Jun 1;37(2):e20-e21.

Altınay M, Karne H, Anand A. Administration of Sub-anesthetic Dose of Ketamine and Electroconvulsive Treatment on Alternate Week Days in Patients with Treatment Resistant Depression: A Double Blind Placebo Controlled Trial. Psychopharmacol Bull. 2019 Feb 15;49(1):8-16.

Ketamine and ECT:



plus

ECT



story of this talk ...



alternating with

ECT



might act a little faster ...

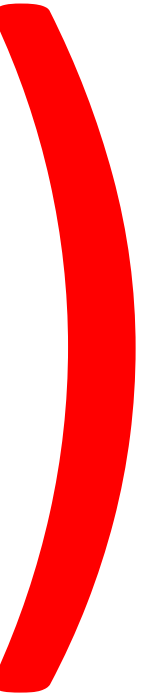


versus

ECT

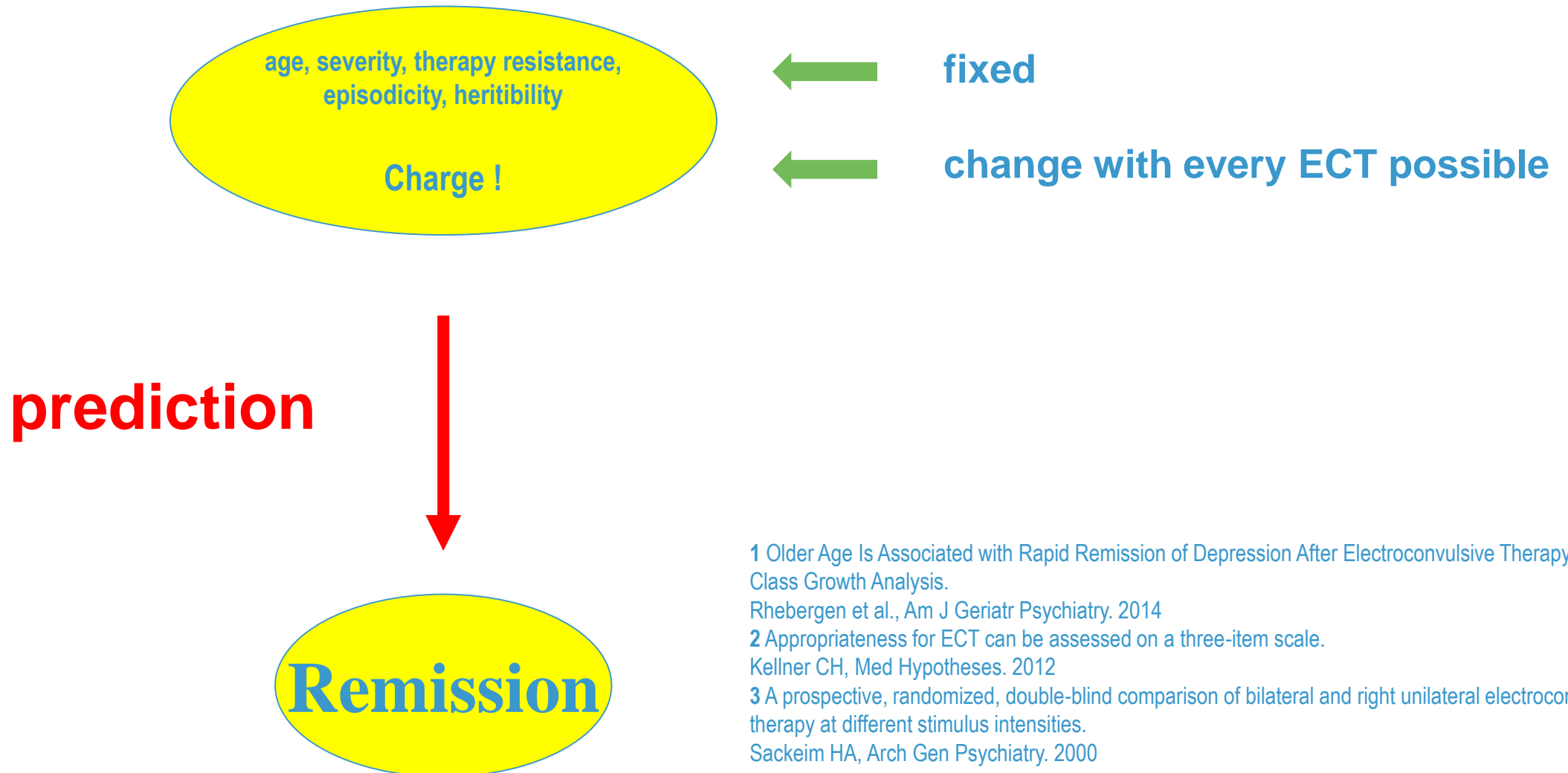


Pouya ! (next talk)

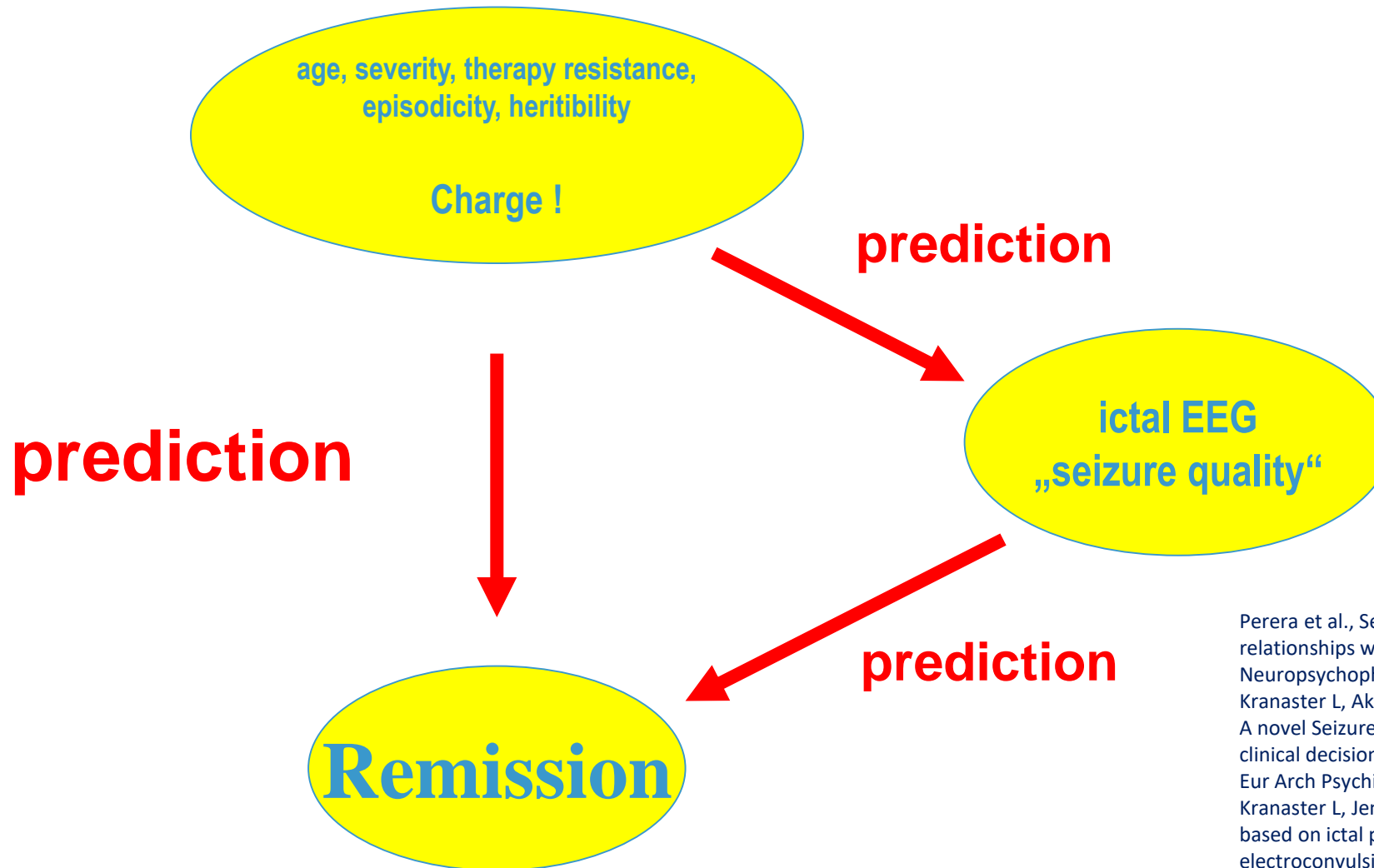


Ketamine and ECT:

Why we would like to quantify seizure quality ?



Ketamine and ECT: Why we would like to quantify seizure quality ?



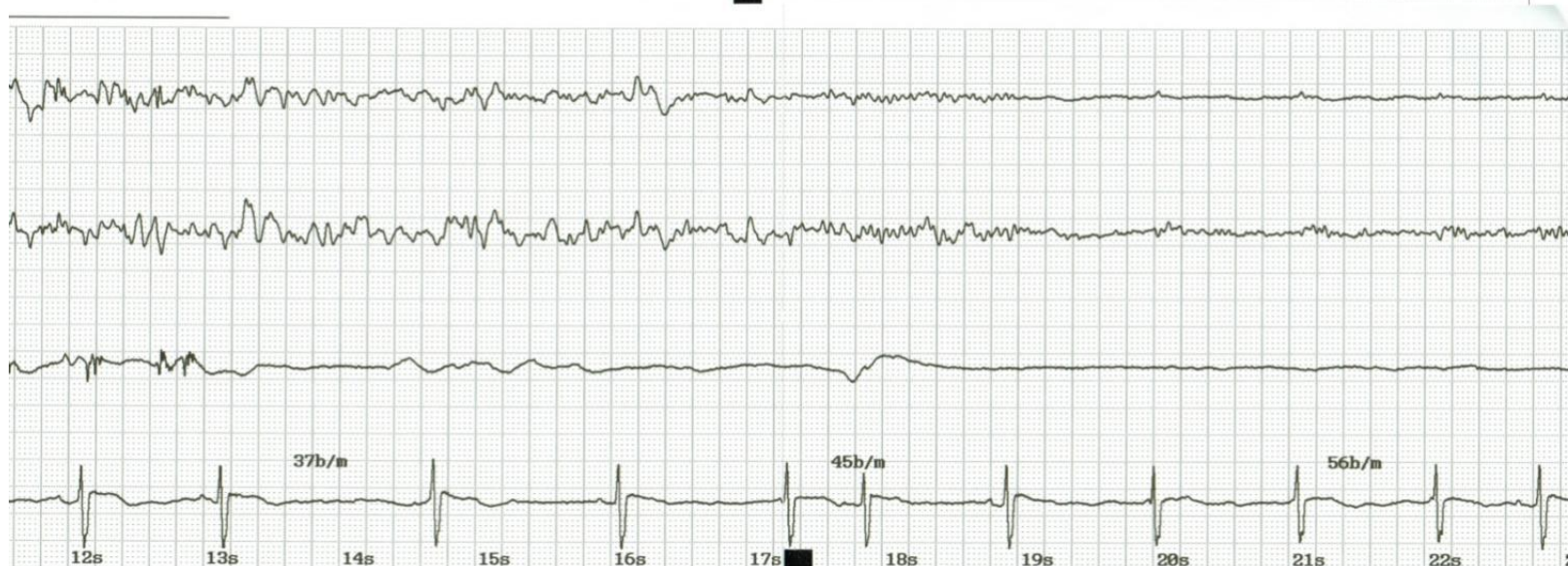
Perera et al., Seizure expression during electroconvulsive therapy: relationships with clinical outcome and cognitive side effects. *Neuropsychopharmacology*. 2004 Apr;29(4):813-25.
Kranaster L, Aksay SS, Bumb JM, Hoyer C, Jennen-Steinmetz C, Sartorius A. A novel Seizure Quality Index based on ictal parameters for optimizing clinical decision making in electroconvulsive therapy. Part 1: development. *Eur Arch Psychiatry Clin Neurosci*. 2018 Dec;268(8):819-830.
Kranaster L, Jennen-Steinmetz C, Sartorius A. A novel seizure quality index based on ictal parameters for optimizing clinical decision-making in electroconvulsive therapy. Part 2: Validation. *Eur Arch Psychiatry Clin Neurosci*. 2019 Oct;269(7):859-865.

Optimising the seizure



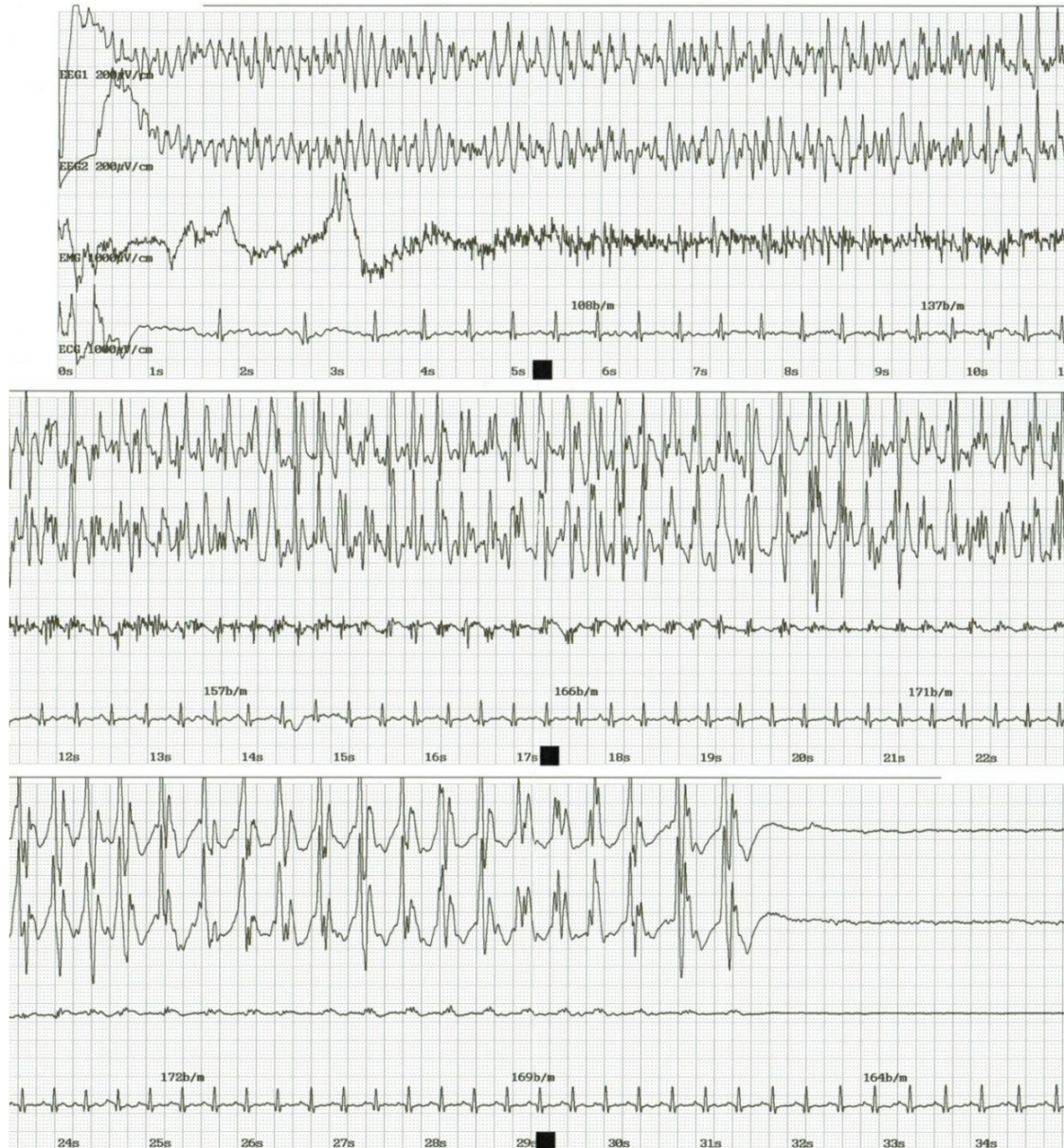
Possible markers:

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



160% RUL

Optimising the seizure



Possible markers:

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

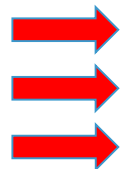
30% RUL

Seizure Duration

Table 2

Mixed effects linear regression of log-transformed seizure duration on sex, age, treatment dose, and treatment number, with a knot placed at the third treatment.

Predictors	Seizure Duration (w/Knot at tx #3)		
	<i>Estimates</i>	<i>CI</i>	<i>p</i>
Sex (male)	-0.02	-0.06 – 0.02	0.265
Age (z-score)	-0.14	-0.16 – -0.12	< 0.001
Dose (z-score)	-0.06	-0.08 – -0.05	< 0.001
Treatment number			
#1 - #3	-0.28	-0.30 – -0.26	< 0.001
#3 - #12	-0.01	-0.02 – -0.01	< 0.001

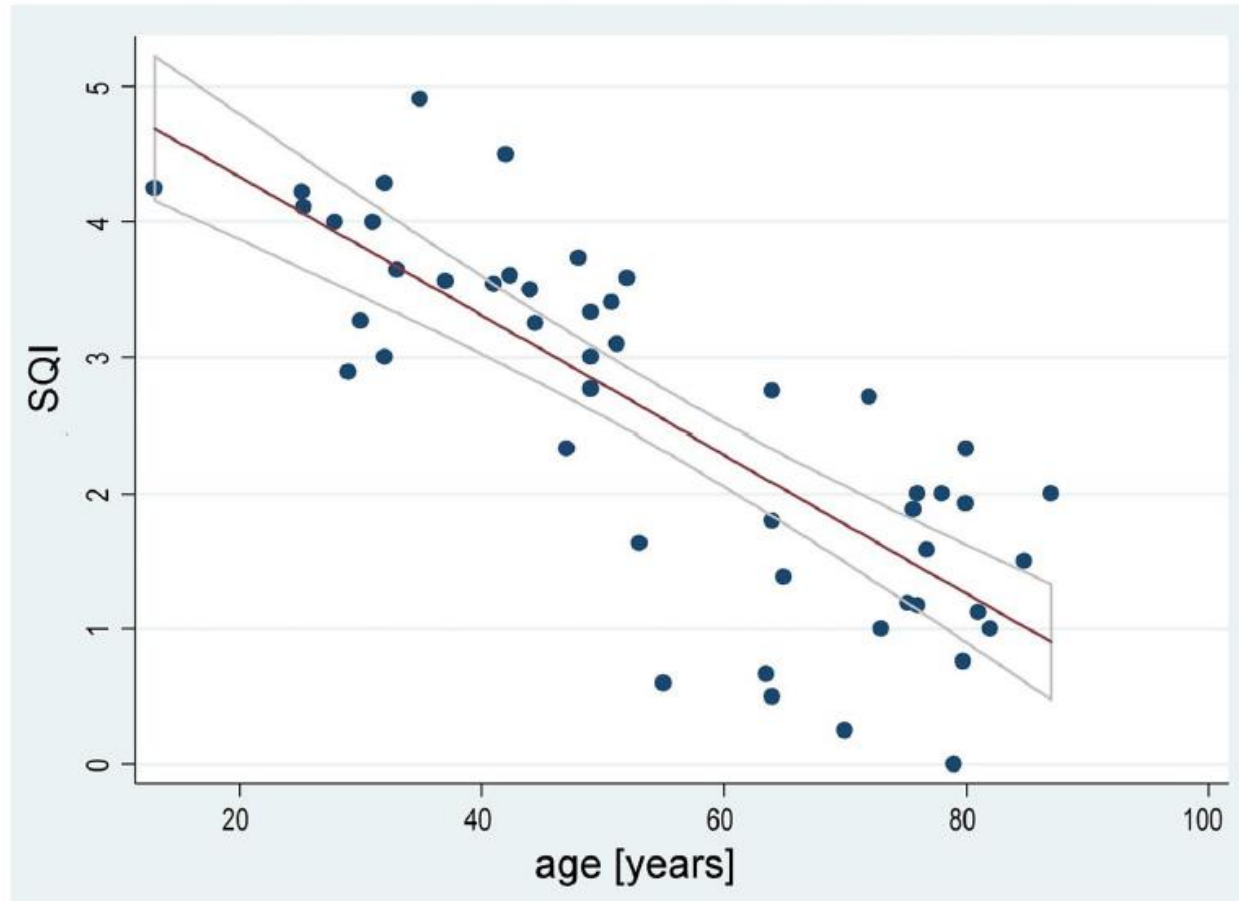


N= 3648 Patients included:

Luccarelli J, McCoy TH Jr, Seiner SJ, Henry ME. Changes in seizure duration during acute course electroconvulsive therapy. *Brain Stimul.* 2021 Jun 11;14(4):941-946.

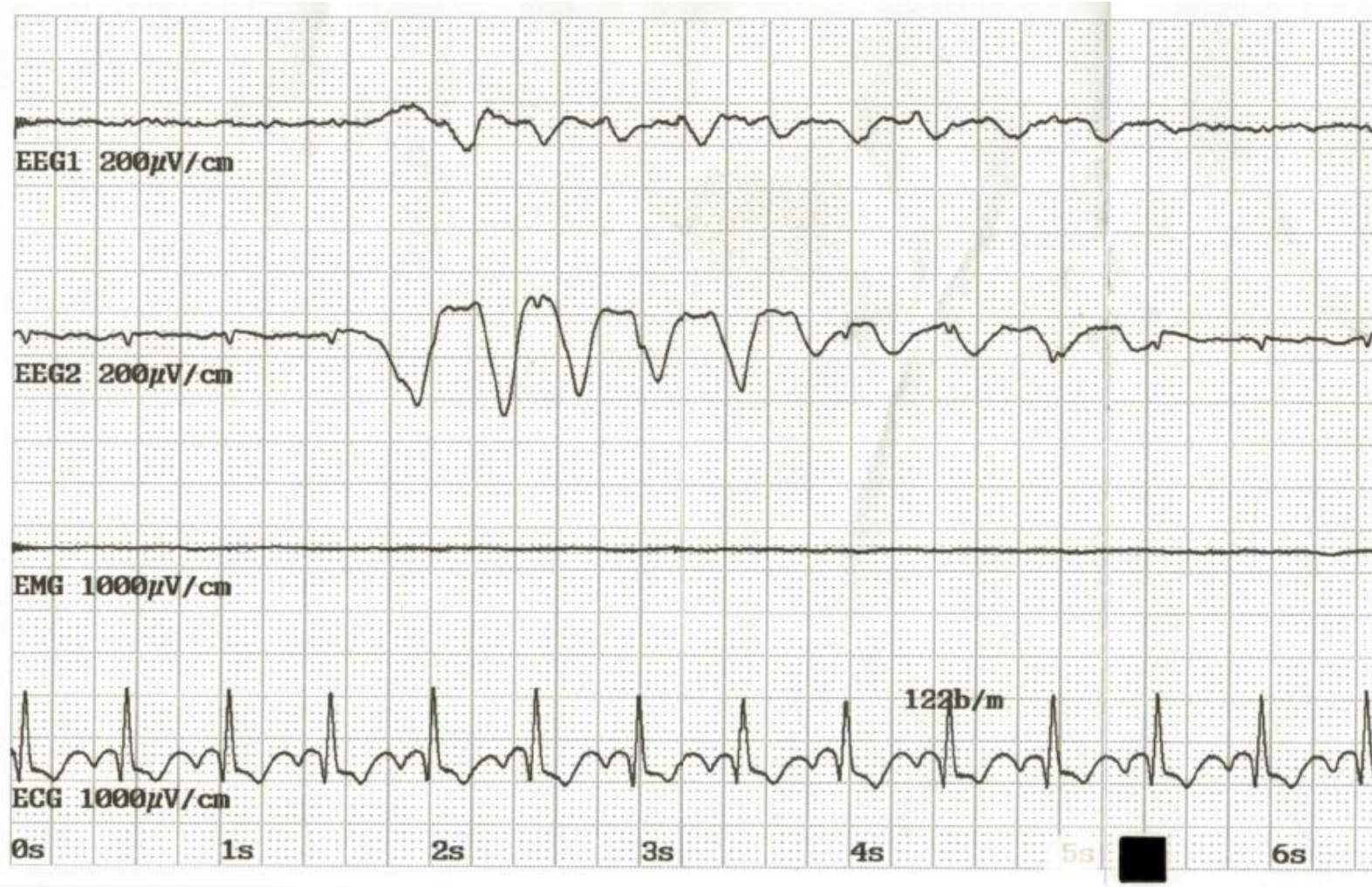
Seizure marks are strongly age dependent

Fig. 1 Negative correlation between age and SQI. Line fits represent linear regression and 95% confidence interval

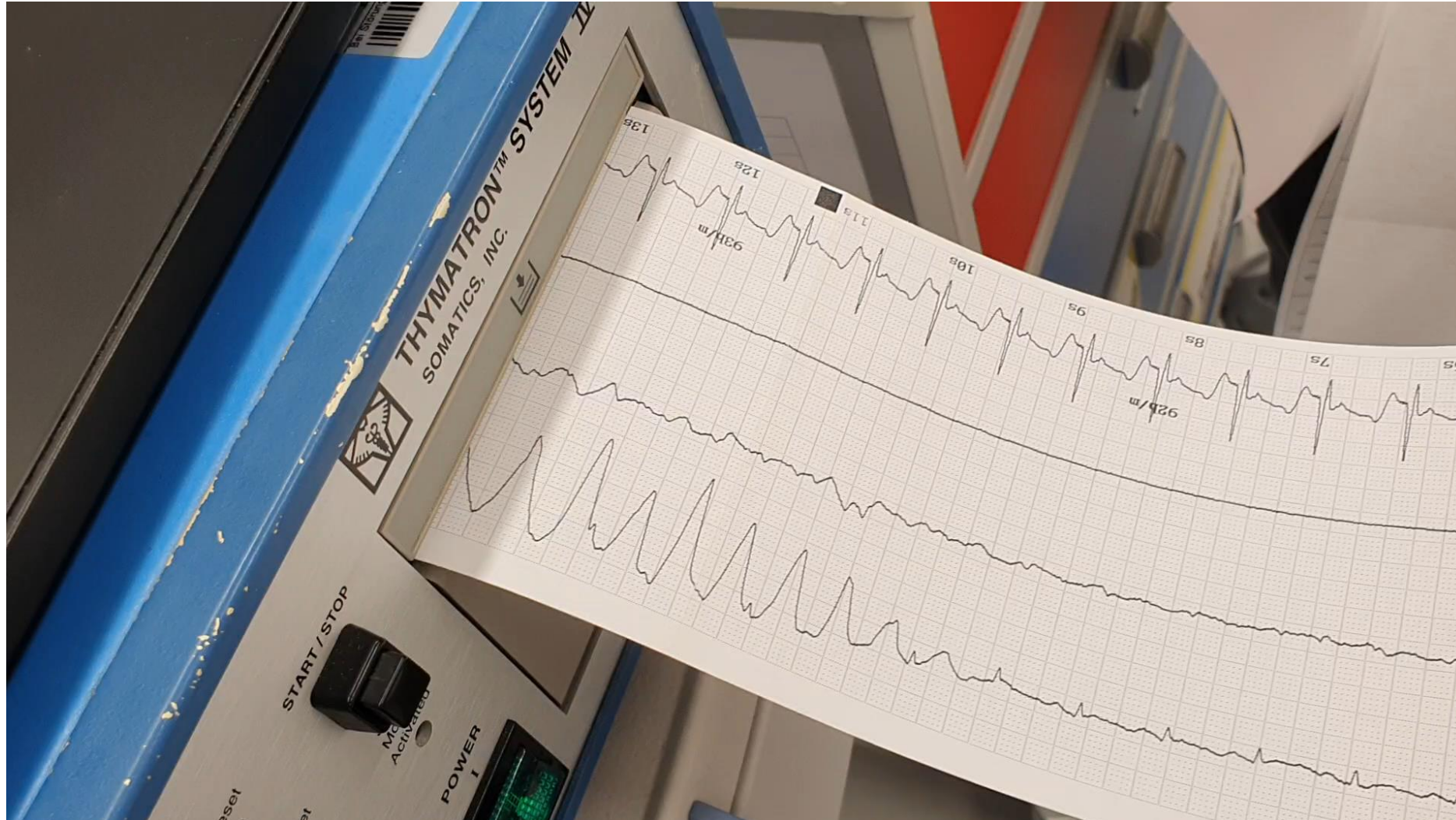


Sartorius A, Beuschlein J, Remennik D, Pfeifer AM, Karl S, Bumb JM, Aksay SS, Kranaster L, Janke C. Empirical ratio of the combined use of S-ketamine and propofol in electroconvulsive therapy and its impact on seizure quality. *Eur Arch Psychiatry Clin Neurosci.* 2021 Apr;271(3):457-463.

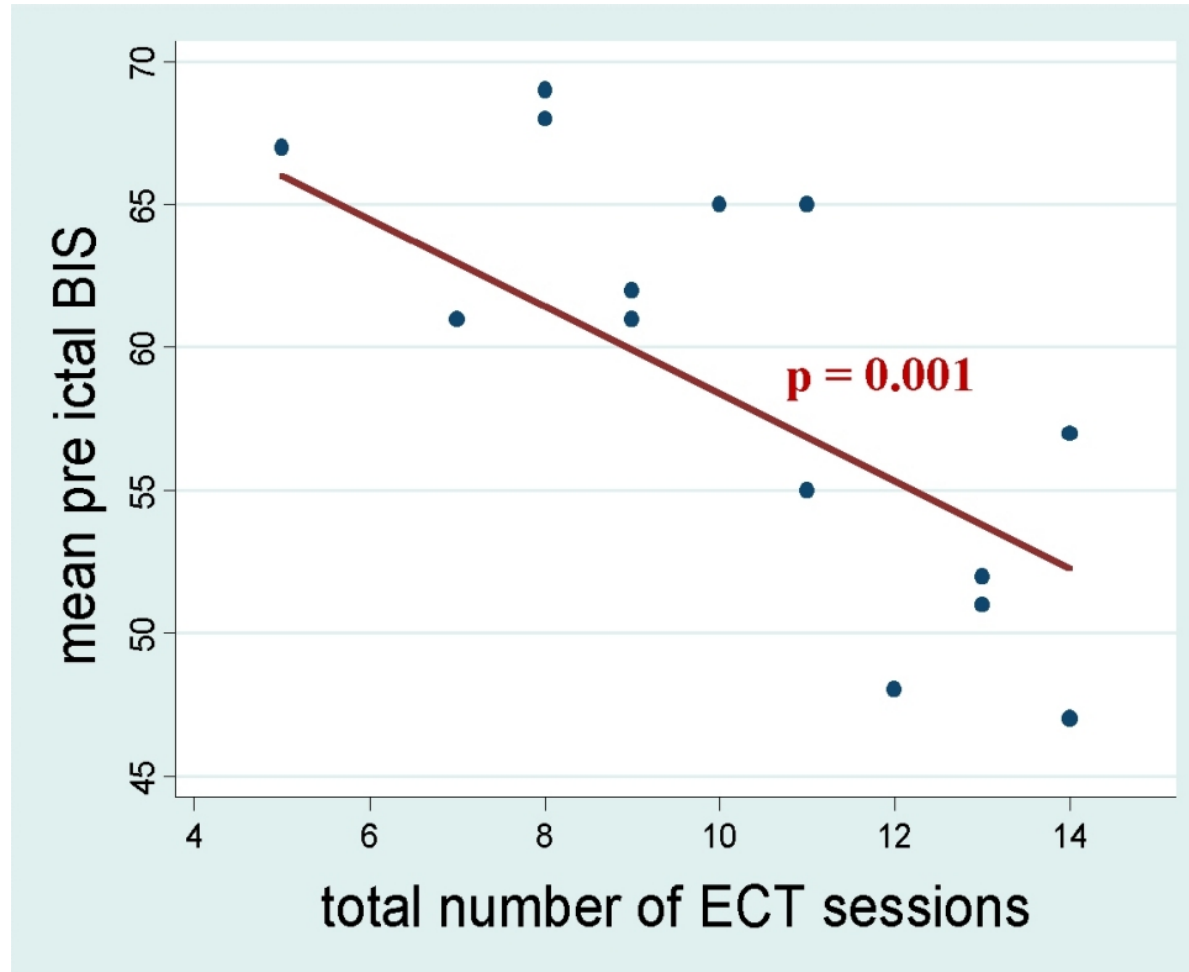
Seizure ?



ECT and the bad anesthesiologist



Outcome and ECT anaesthesia - thiopental



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

Outcome and ECT anaesthesia: Thiopental / Propofol => Response

	<i>N</i> included	Response/remission/memory worsening, %	Crude odds ratio (95% CI)	<i>P</i> -value	Adjusted odds ratio (95% CI)	<i>P</i> -value
Response, CGI-I						
Low-dose interval	3140	75.7%	1.27 (1.11–1.45)	<0.001	1.22 (1.07–1.40)	0.004
Medium-dose interval	2266	74.8%	1.21 (1.05–1.39)	0.008	1.15 (1.00–1.33)	0.056
High-dose interval	1805	71.1%	Reference	Reference	Reference	Reference
Distinct response, CGI-I						
Low-dose interval	3140	32.7%	1.60 (1.40–1.83)	<0.001	1.51 (1.32–1.73)	<0.001
Medium-dose interval	2266	29.4%	1.37 (1.19–1.58)	<0.001	1.32 (1.14–1.53)	<0.001
High-dose interval	1805	23.3%	Reference	Reference	Reference	Reference
Remission, CGI-S						
Low-dose interval	2950	23.0%	1.48 (1.27–1.72)	<0.001	1.37 (1.17–1.60)	<0.001
Medium-dose interval	2134	21.6%	1.36 (1.16–1.60)	<0.001	1.30 (1.10–1.54)	0.002
High-dose interval	1716	16.8%	Reference	Reference	Reference	Reference
Response, MADRS-S						
Low-dose interval	1470	65.4%	1.39 (1.17–1.65)	<0.001	1.31 (1.09–1.56)	0.004
Medium-dose interval	1026	60.7%	1.13 (0.94–1.36)	0.180	1.06 (0.87–1.28)	0.556
High-dose interval	889	57.7%	Reference	Reference	Reference	Reference
Remission, MADRS-S						
Low-dose interval	1801	43.9%	1.45 (1.24–1.70)	<0.001	1.31 (1.11–1.55)	0.002
Medium-dose interval	1210	39.7%	1.22 (1.03–1.45)	0.023	1.13 (0.94–1.36)	0.18
High-dose interval	1031	35.0%	Reference	Reference	Reference	Reference
Subjective memory worsening						
Low-dose interval	1923	21.6%	1.34 (1.11–1.62)	0.002	1.32 (1.09–1.60)	0.004
Medium-dose interval	1398	17.0%	1.00 (0.81–1.22)	0.971	0.99 (0.80–1.22)	0.893
High-dose interval	1176	17.0%	Reference	..	Reference	..

dose-dependent response and remission

For each outcome, the table shows the number of included patients (if patients had missing data on the outcome they were excluded from the logistic regression models). The proportion of each outcome. Crude odds ratios and their 95% confidence intervals were calculated by correlating the age and gender-adjusted dose intervals and the outcomes without any further variables. A regression model adjusted for age, gender, number of treatments, psychiatric comorbidity and psychiatric pharmacotherapy was used to calculate adjusted odds ratios and their 95% confidence intervals. *P*-values are shown for both crude and adjusted odds ratios separately. CGI-S, Clinical Global Impression – Severity Scale; CGI-I, Clinical Global Impression – Improvement Scale; MADRS-S, Montgomery–Åsberg Depression Rating Scale, self-rated version.

thiopental (64.1%) or propofol (35.9%)

ECT anaesthesia



substance	typical dose range (mg/kg)	anticonvulsive effect (relative)	remarks
methohexital	0,75-1.0	1-2	former gold standard, cardiovascular depression
thiopental	2-5	2	cardiovascular depression
propofol	1-2	3	shorter seizures, higher seizure threshold
etomidate	0.2-0.3	0	myocloni
S-ketamine	0.5-1.5	0	low doses pro-psychotic, higher blood pressure
alfentanil	0.01-0.015	0	longer time of apnoe, cardiovascular depression
remifentanil	0.001-0.008	1	similar to alfentanil ?

* **Black Box Warning**
 ** **Rote-Hand-Briefe**

* Hikma Pharmaceuticals stopped the production of methohexital 2019-2022
 ** Good Manufacturing Practice (GMP) problems at Lampugnani Pharmaceutici SPA
 *** In Germany: more or less obsolete for critically ill patients and for non-single induction use

Adapted from:

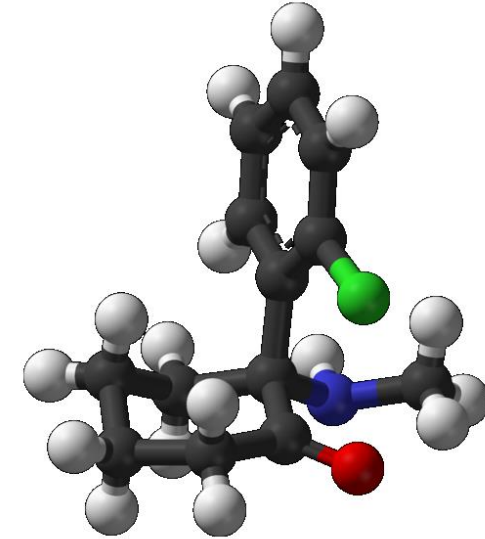
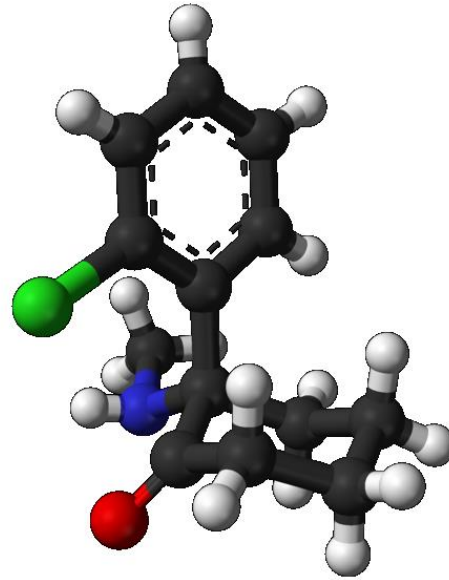
Folkerts HW.
 Electroconvulsive therapy. Indications, procedure and treatment results
 Nervenarzt. 2011 Jan;82(1):93-102

Swartz CM
 Electroconvulsive and neuromodulation therapies.
 2009 Cambridge Univ, Cambridge New York Melbourne

ECT anaesthesia - ketamine

ketamine in general anesthesia:

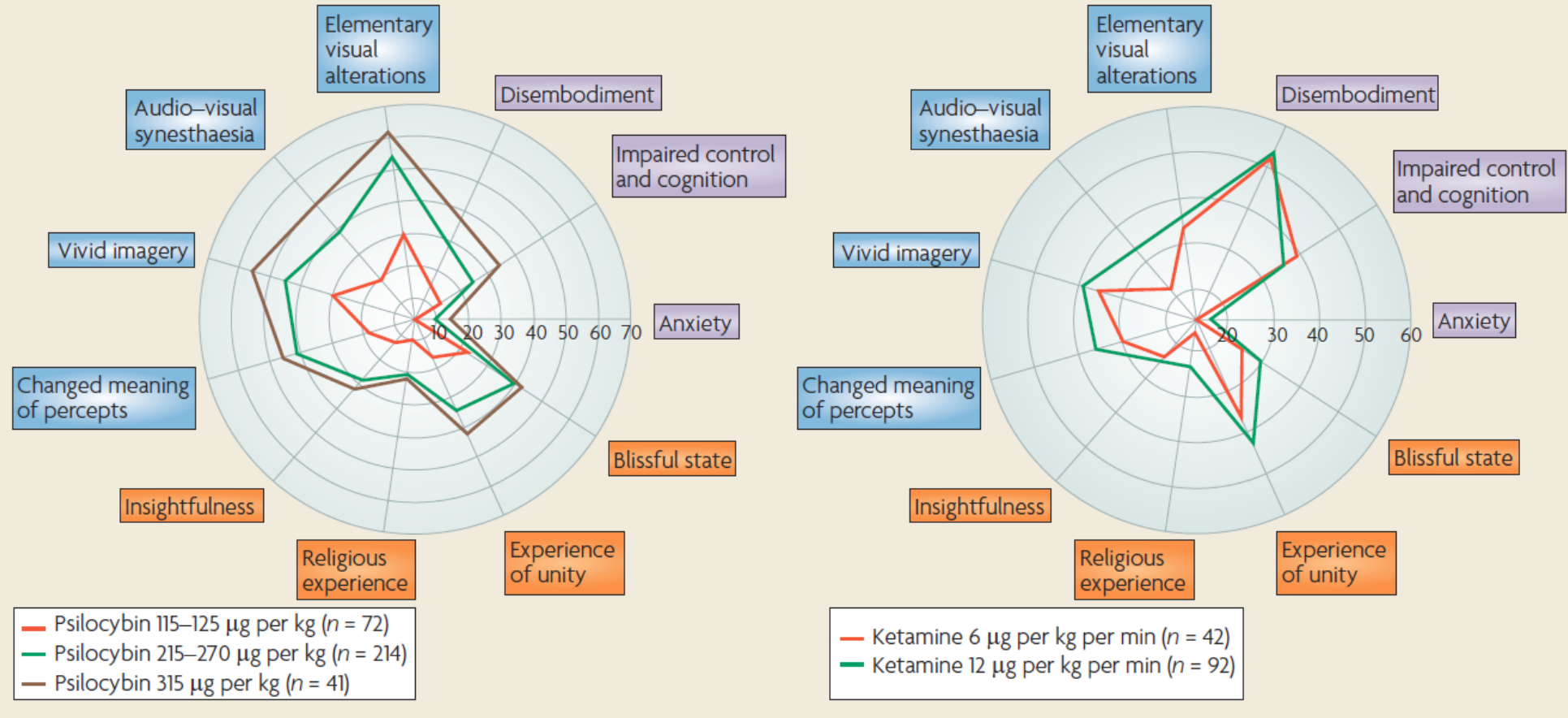
- is listed as an essential drug by the WHO
- often used in emergency medicine
- treatment of status asthmaticus
- analgesia of intubated patients
- preferred for children and adolescents
- still in use for general and regional anesthesia (alone and in combination with hypnotics)
- off-label for chronic pain patients



ECT anaesthesia: Ketamine

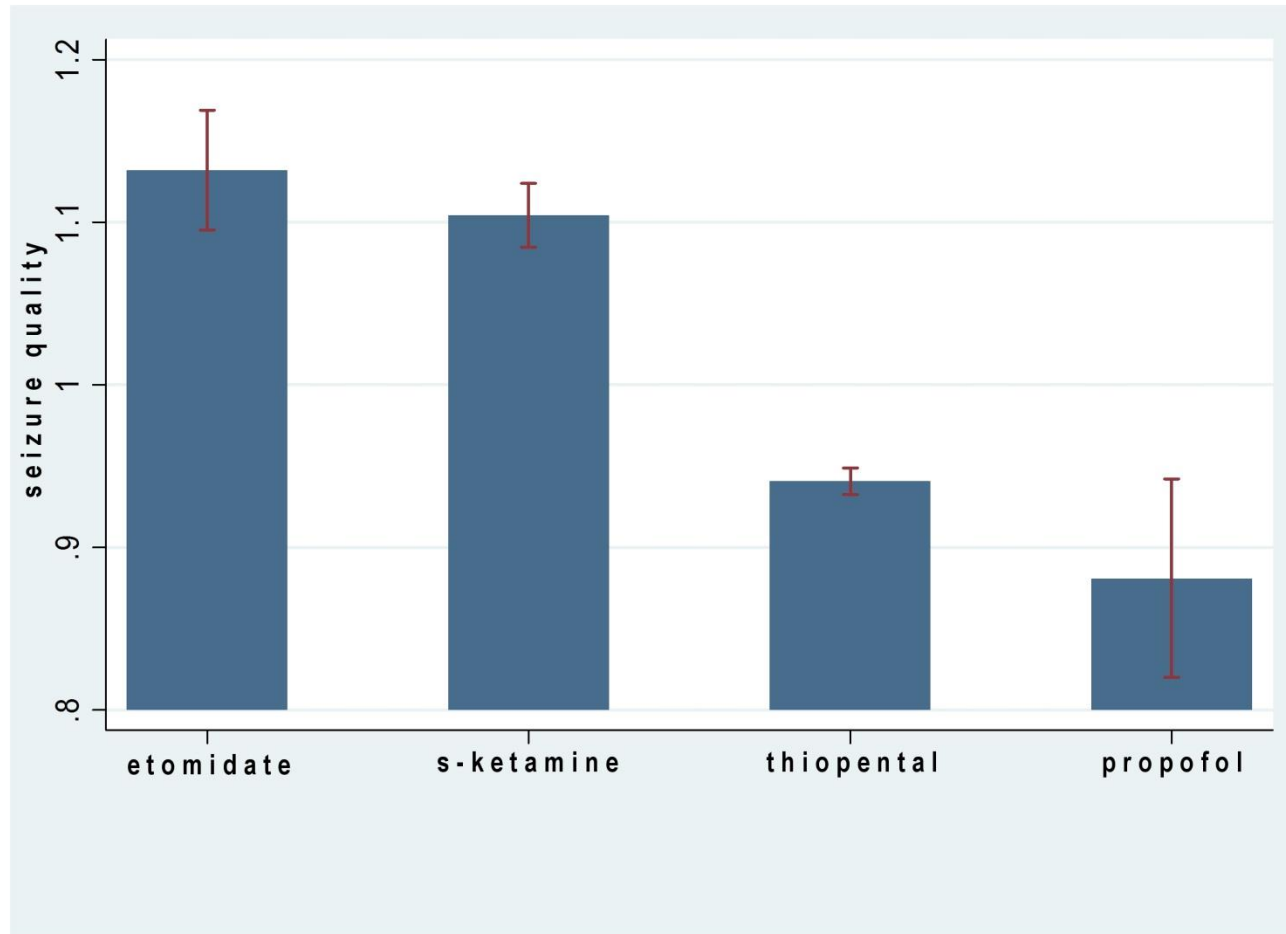


Box 1 | Assessing altered states of consciousness



The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. Vollenweider FX, Kometer M. Nat Rev Neurosci. 2010 Sep;11(9):642-51.

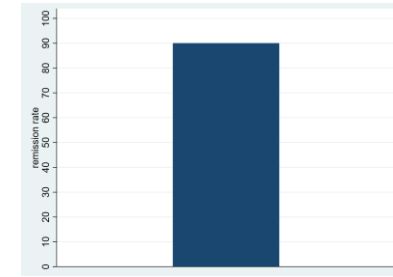
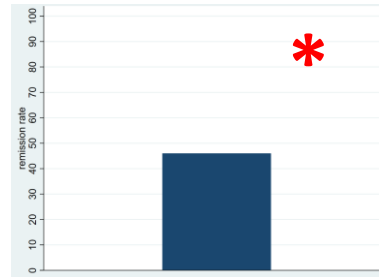
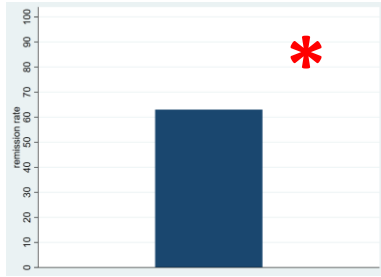
ECT anaesthesia - ketamine



Impact of ketamine, etomidate, thiopental and propofol as anesthetic on seizure parameters and seizure quality in electroconvulsive therapy: A retrospective study
Carolin Hoyer, Laura Kranaster, Christoph Janke, Alexander Sartorius
Eur Arch Psychiatry Clin Neurosci 2014 Apr;264(3):255-61.

Does Ketamine improve ECT ?

ECT



* “In total 186 inpatients were included and received treatment. Among patients receiving ECT, 63% remitted compared with 46% receiving ketamine infusions”.

... maybe even 90% remission ? ...

Ekstrand J, Fattah C, Persson M, Cheng T, Nordanskog P, Åkeson J, Tingström A, Lindström MB, Nordenskjöld A, Movahed Rad P. Racemic Ketamine as an Alternative to Electroconvulsive Therapy for Unipolar Depression: A Randomized, Open-Label, Non-Inferiority Trial (KetECT). *Int J Neuropsychopharmacol.* 2022 May 27;25(5):339-349

Does Ketamine improve ECT ?

Thus – hypothetically – there are 2 good reasons why it should:

- Ketamine does not increase seizure threshold – since it is no anticonvulsant
- Ketamine acts as an antidepressant itself

Does Ketamine improve ECT ?

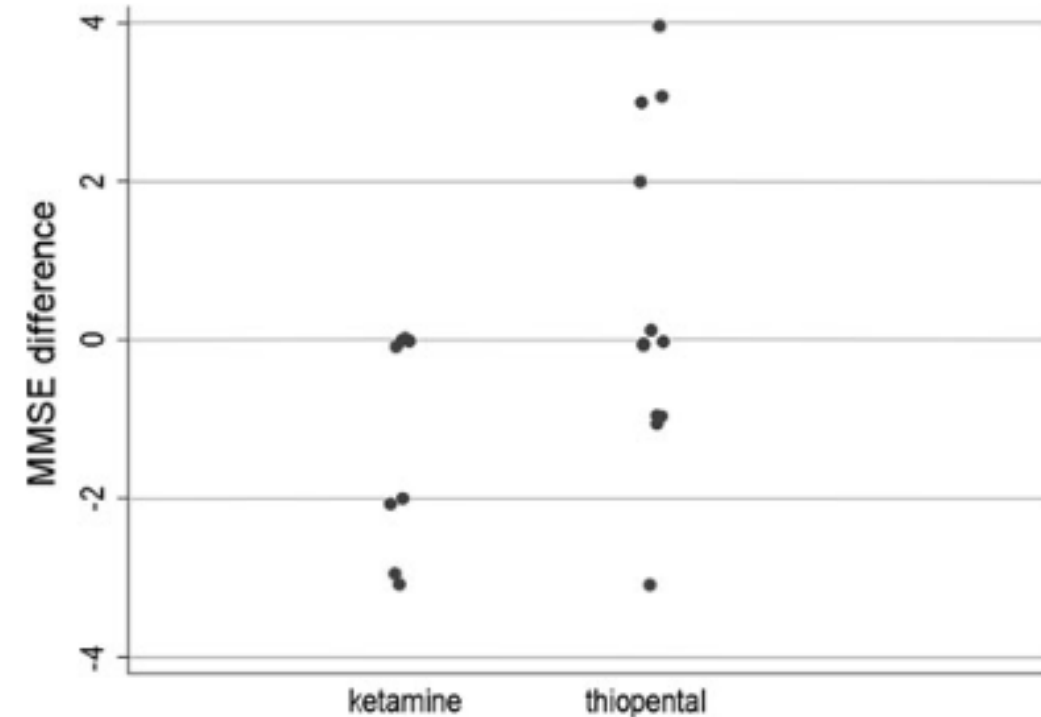
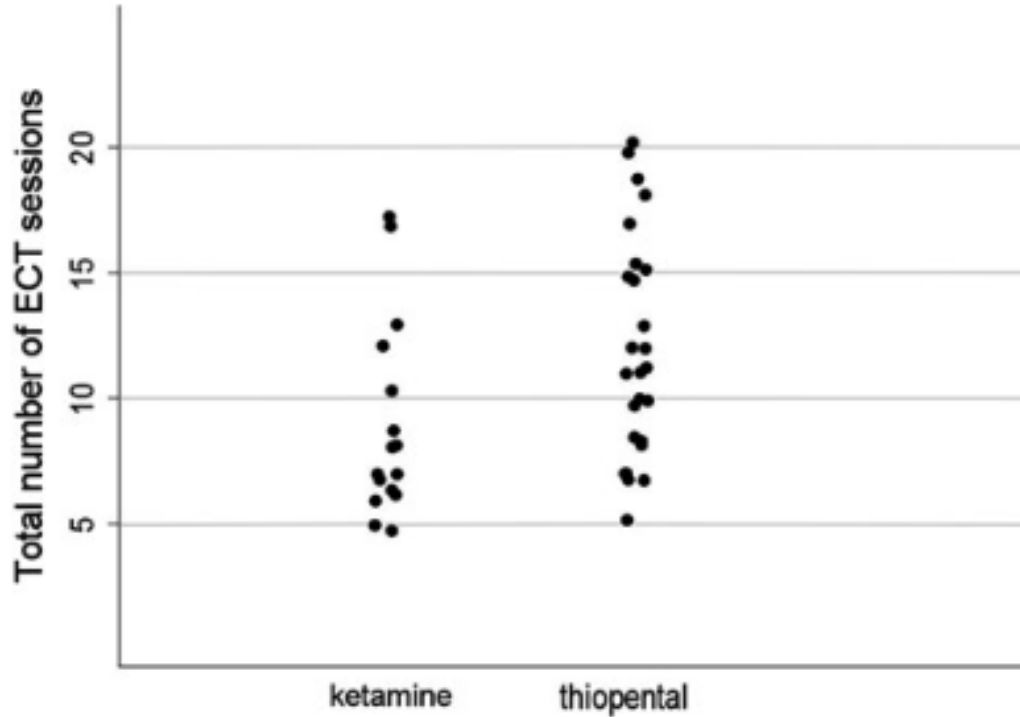
Abstract

The authors retrospectively compared the seizure duration, ictal EEG, and cognitive side effects of ketamine and methohexital anesthesia with ECT. This comparison was carried out with data from consecutive index ECT treatments that occurred immediately before and after a switch from methohexital to ketamine in 36 patients. Ketamine was well tolerated and prolonged seizure duration overall, but particularly in those who had a seizure duration shorter than 25 seconds with methohexital at the maximum available stimulus intensity. Ketamine also increased midictal EEG slow-wave amplitude.

Thus, a switch to ketamine may be useful when it is difficult to elicit a robust seizure. Faster post-treatment reorientation with ketamine may suggest a lower level of associated cognitive side effects.

Krystal AD, Weiner RD, Dean MD, Lindahl VH, Tramontozzi LA 3rd, Falcone G, Coffey CE. Comparison of seizure duration, ictal EEG, and cognitive effects of ketamine and methohexital anesthesia with ECT. J Neuropsychiatry Clin Neurosci. 2003 Winter;15(1):27-34.

Does Ketamine improve ECT ?



Kranaster L, Kammerer-Ciernioch J, Hoyer C, Sartorius A. Clinically favourable effects of ketamine as an anaesthetic for electroconvulsive therapy: a retrospective study. *Eur Arch Psychiatry Clin Neurosci.* 2011 Dec;261(8):575-82.

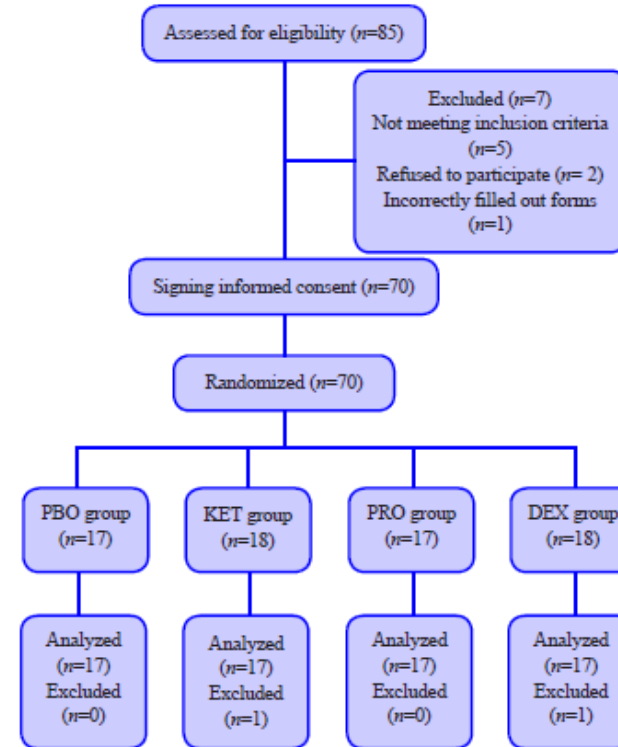
Does Ketamine improve ECT ? => add-on studies...

two recent examples

RCT (n=45):

propofol at 1.2 mg/kg
plus
0.2 mg/kg or 0.5 mg/kg

=> No differences.

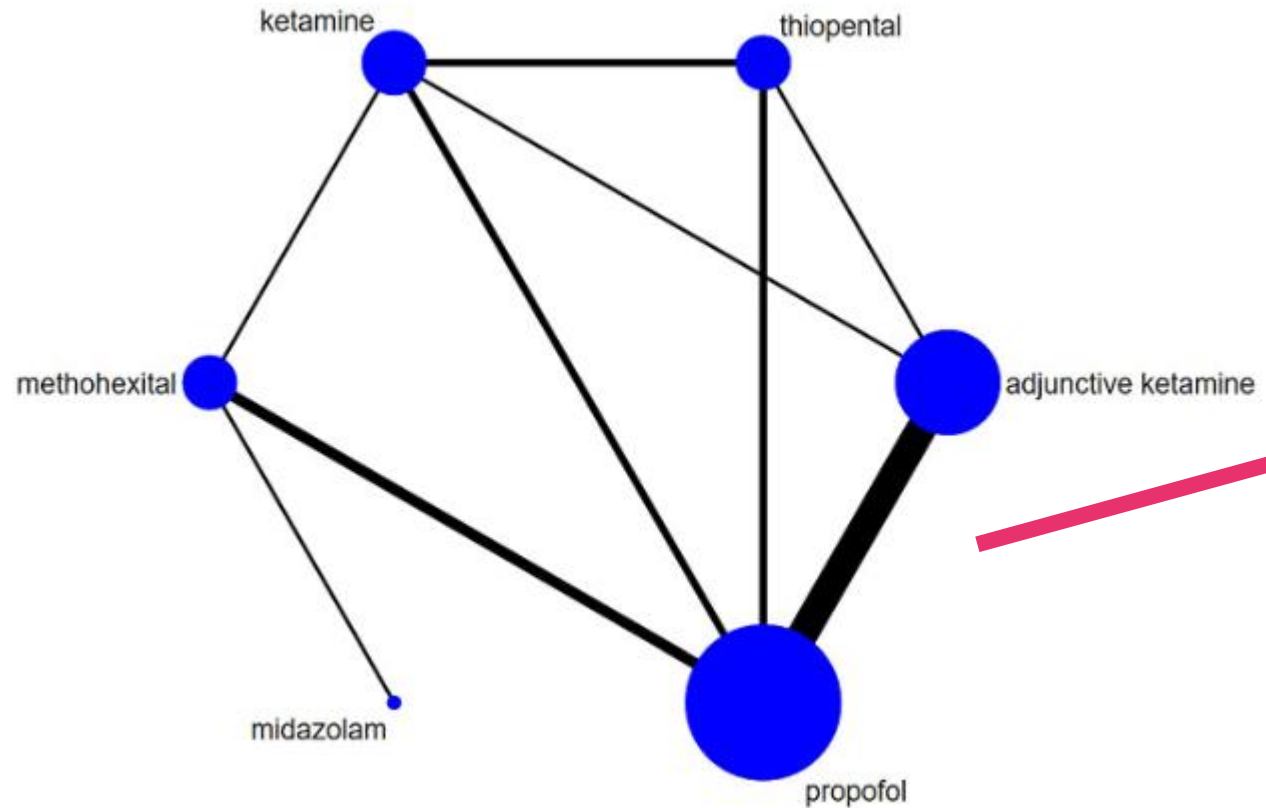


- „thiopental 1.5–3 mg/kg”
- “30–100 joules of electric shock”

Woolsey AJ, Nanji JA, Moreau C, Sivapalan S, Bourque SL, Ceccherini-Nelli A, Gragasin FS. Low-dose ketamine does not improve the speed of recovery from depression in electroconvulsive therapy: a randomized controlled trial. *Braz J Psychiatry*. 2022 Jan-Feb;44(1):6-14.

Modir H, Mahmoodiyeh B, Shayganfard M, Abdus A, Almasi-Hashiani A. Efficacy of ketamine, propofol, and dexmedetomidine for anesthesia in electroconvulsive therapy in treatment-resistant major depressive disorder patients: a double-blind randomized clinical trial. *Med Gas Res*. 2023 Jul-Sep;13(3):112-117.

Does Ketamine improve ECT ?



results from just „adding“ another substance are quite evident:

- no improvements
- more side effects

Ren L, Yu J, Zeng J, Wei K, Li P, Luo J, Shen Y, Lv F, Min S. Comparative efficacy and tolerability of different anesthetics in electroconvulsive therapy for major depressive disorder: A systematic review and network meta-analysis. J Psychiatr Res. 2024 Mar;171:116-125.

ECT anaesthesia – ketamine – at least faster than propofol

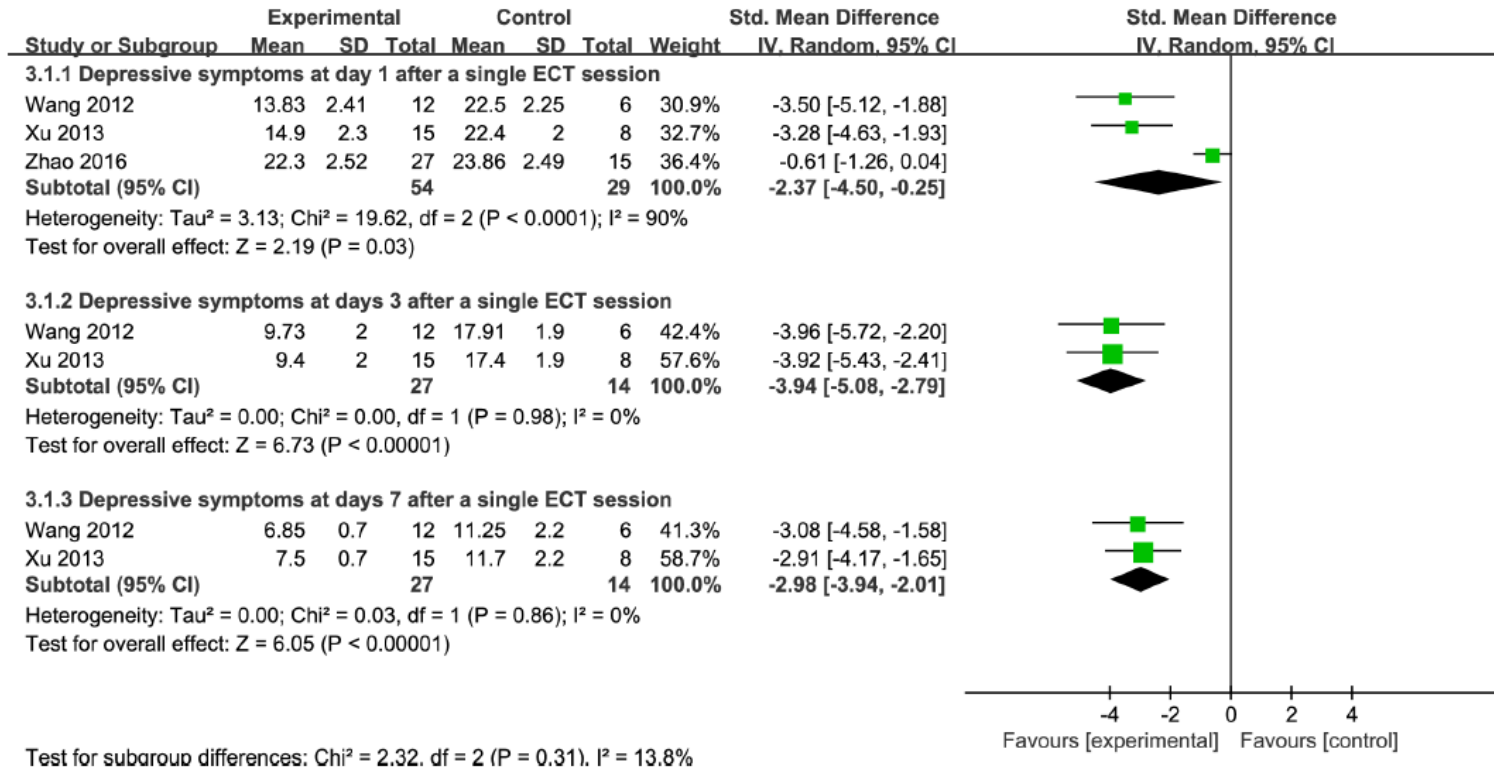
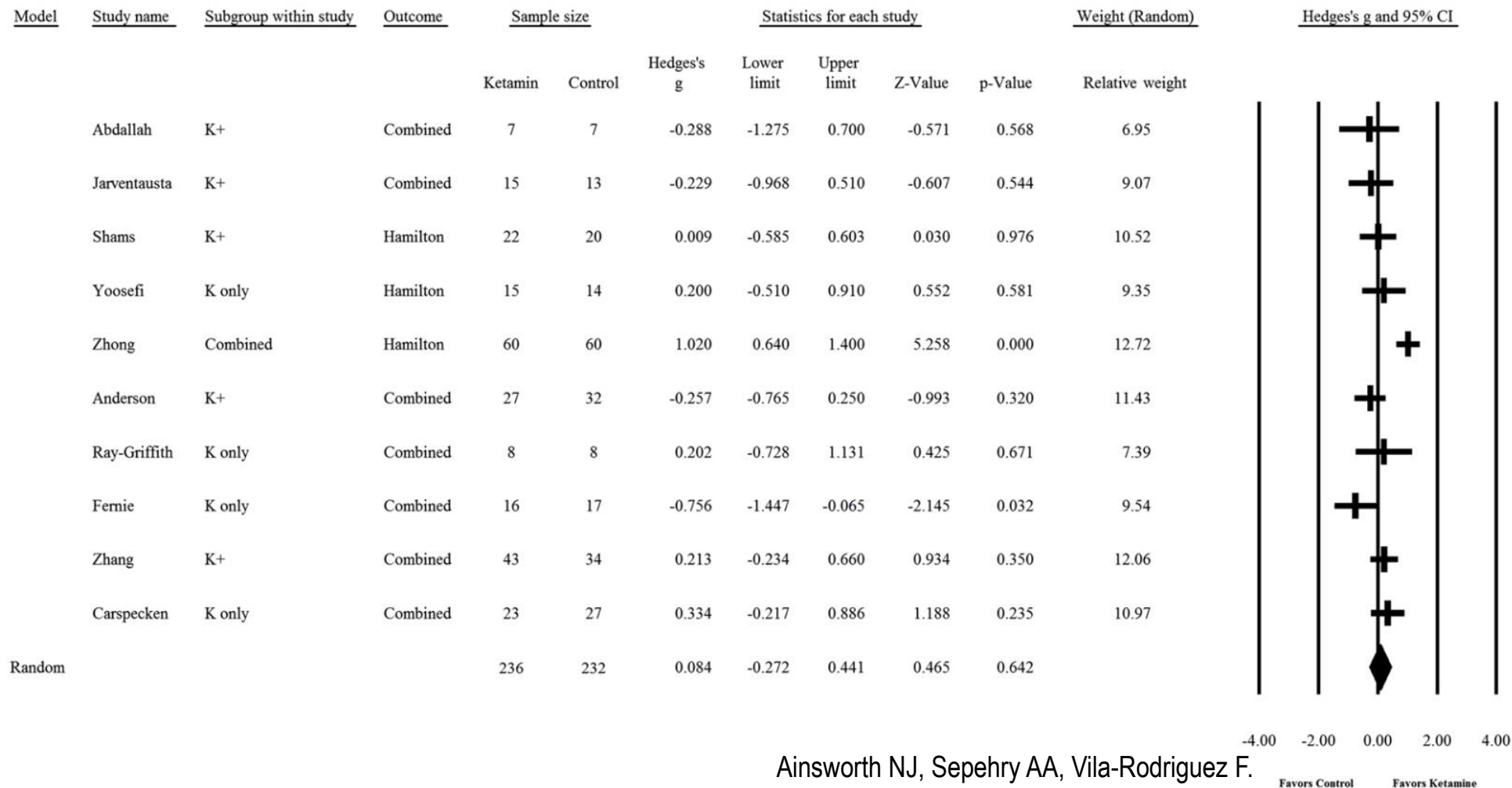


Figure 2 The ketamine group versus the propofol group: forest plot for depressive symptoms at days 1, 3 and 7 after a single electroconvulsive therapy session.

Li XM, Shi ZM, Wang PJ, Hu H. Effects of ketamine in electroconvulsive therapy for major depressive disorder: meta-analysis of randomised controlled trials. *Gen Psychiatr.* 2020;33(3):e100117.

ECT and ketamine - response



Ainsworth NJ, Sepehry AA, Vila-Rodriguez F.
 Effects of Ketamine Anesthesia on Efficacy, Tolerability, Seizure Response, and Neurocognitive Outcomes in Electroconvulsive Therapy:
 A Comprehensive Meta-analysis of Double-Blind Randomized Controlled Trials.
 J ECT. 2020 Jun;36(2):94-105.

ECT anaesthesia – ketamine – dose (charge)

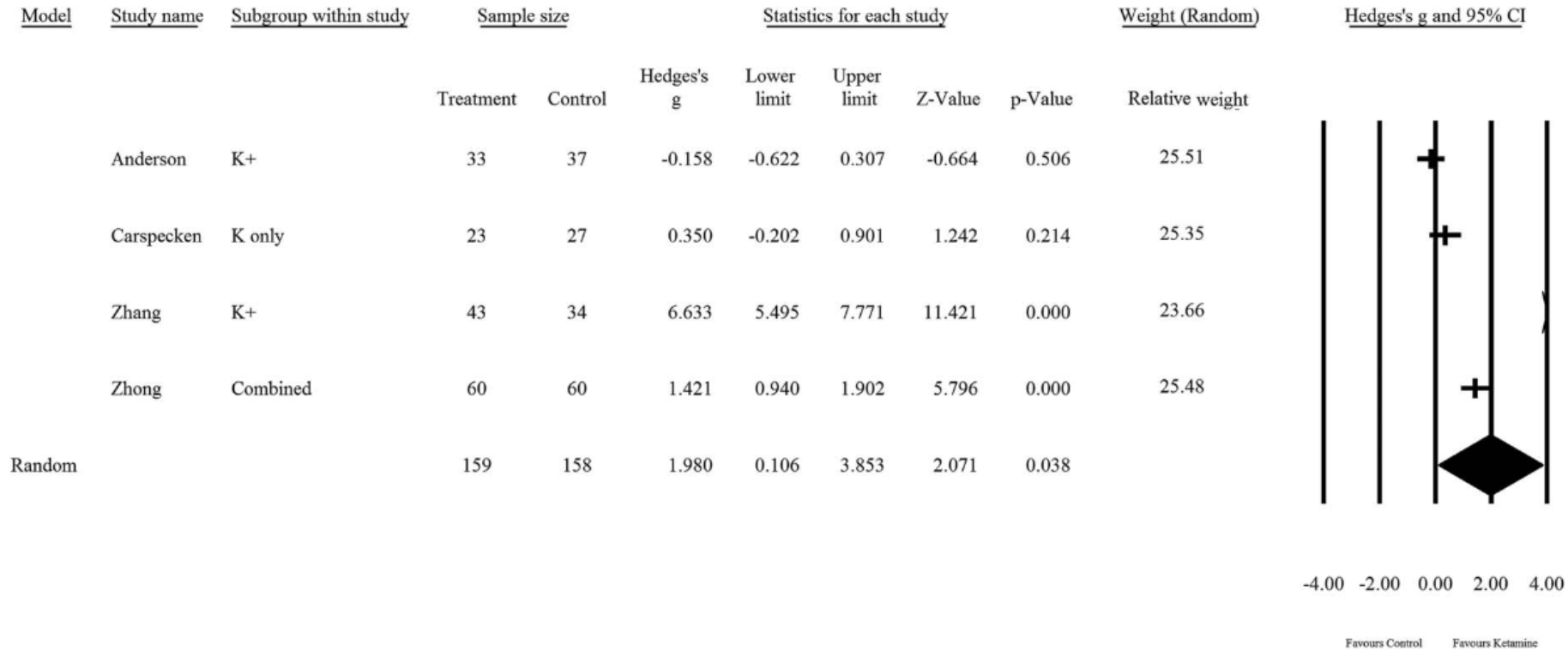


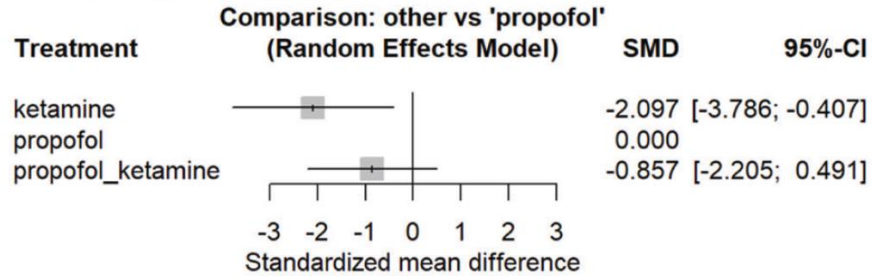
FIGURE 5. Forest plot of meta-analysis results for electrical dose. Numbers along x axis of graph denote effect size as Hedge's *g*; results to the right favor ketamine. Diamond edges denote 95% confidence interval. Z value and P value represent the test for overall effect. Relative weight is expressed as percent of total. K only, patient groups receiving ketamine as sole anesthetic; K+, patient groups receiving ketamine in combination with another anesthetic; combined, results pooled from both K+ and K only groups in study.

Ainsworth NJ, Sepehry AA, Vila-Rodriguez F.
 Effects of Ketamine Anesthesia on Efficacy, Tolerability, Seizure Response, and Neurocognitive Outcomes in Electroconvulsive Therapy:
 A Comprehensive Meta-analysis of Double-Blind Randomized Controlled Trials.
 J ECT. 2020 Jun;36(2):94-105.

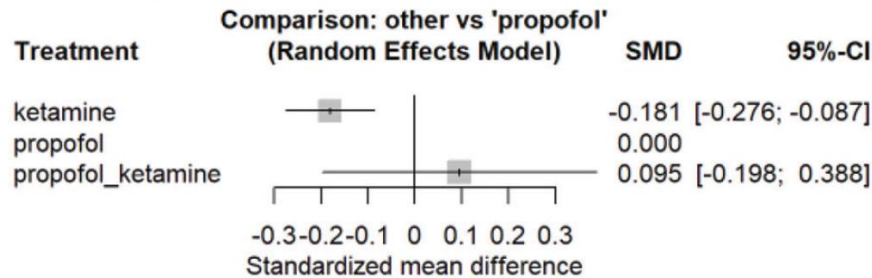
Does Ketamine improve ECT ? Latest Meta-Analysis



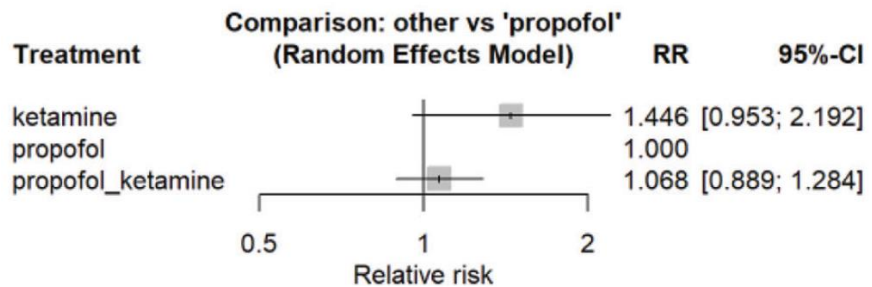
A. Depressive symptoms



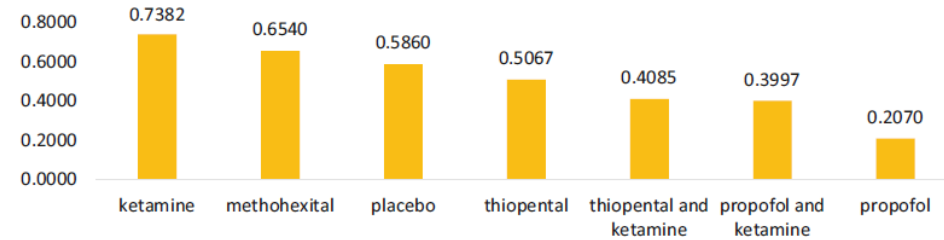
B. Cognition



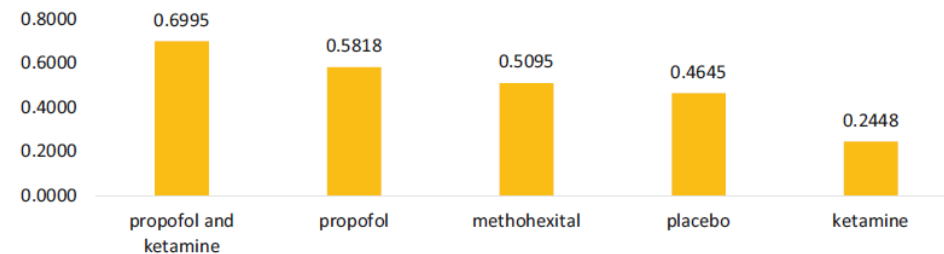
C. Remission



A. Depressive symptoms



B. Cognitive performance



C. Remission

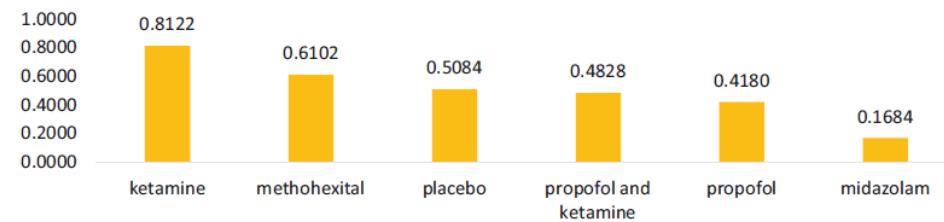


Fig. 4 Rankograms of surface under the cumulative ranking (SUCRA) curves by each outcome measure. A Depressive symptoms. B Cognitive performance. C Remission. D Response. E Serious adverse events. Note: Graphical summary of P-scores of different interventions in the course of electroconvulsive therapy for major depressive episode. Higher and closer-to-1 P-scores indicate greater likelihood of top-rank interventions. Placebo refers to "thiopental plus saline"

Rhee TG, Shim SR, Popp JH, Trikalinos TA, Rosenheck RA, Kellner CH, Seiner SJ, Espinoza RT, Forester BP, McIntyre RS. Efficacy and safety of ketamine-assisted electroconvulsive therapy in major depressive episode: a systematic review and network meta-analysis. Mol Psychiatry. 2023 Dec 20.

taking up a lance for “ketofol”

Take home from own study:

- Propofol still negatively impacts SQI at doses as low as
- Empirical ratio of S-Ketamin / propofol was

0.5mg/kg bw.

3 : 2



**reduce
propofol !!!**

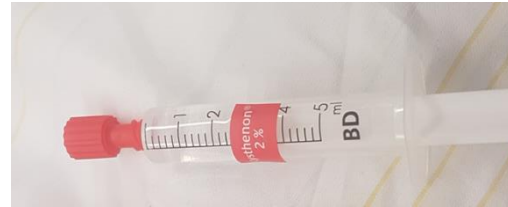
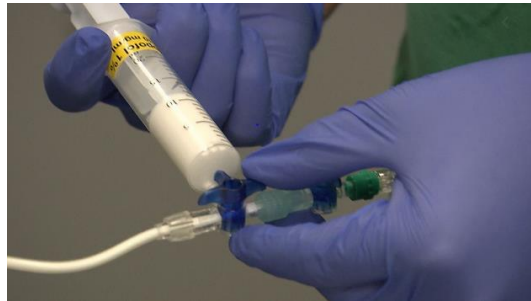
Sartorius A, Beuschlein J, Remennik D, et al. Empirical ratio of the combined use of S-ketamine and propofol in electroconvulsive therapy and its impact on seizure quality [published online ahead of print, 2020 Jul 22]. *Eur Arch Psychiatry Clin Neurosci*.

ECT anaesthesia – ASTI if propofol is still applied



propofol /
thiopental /
methohexital

succinylcholine



1-2 mins



2 - 3 mins



> 4 mins

Optimising the seizure (and the outcome)



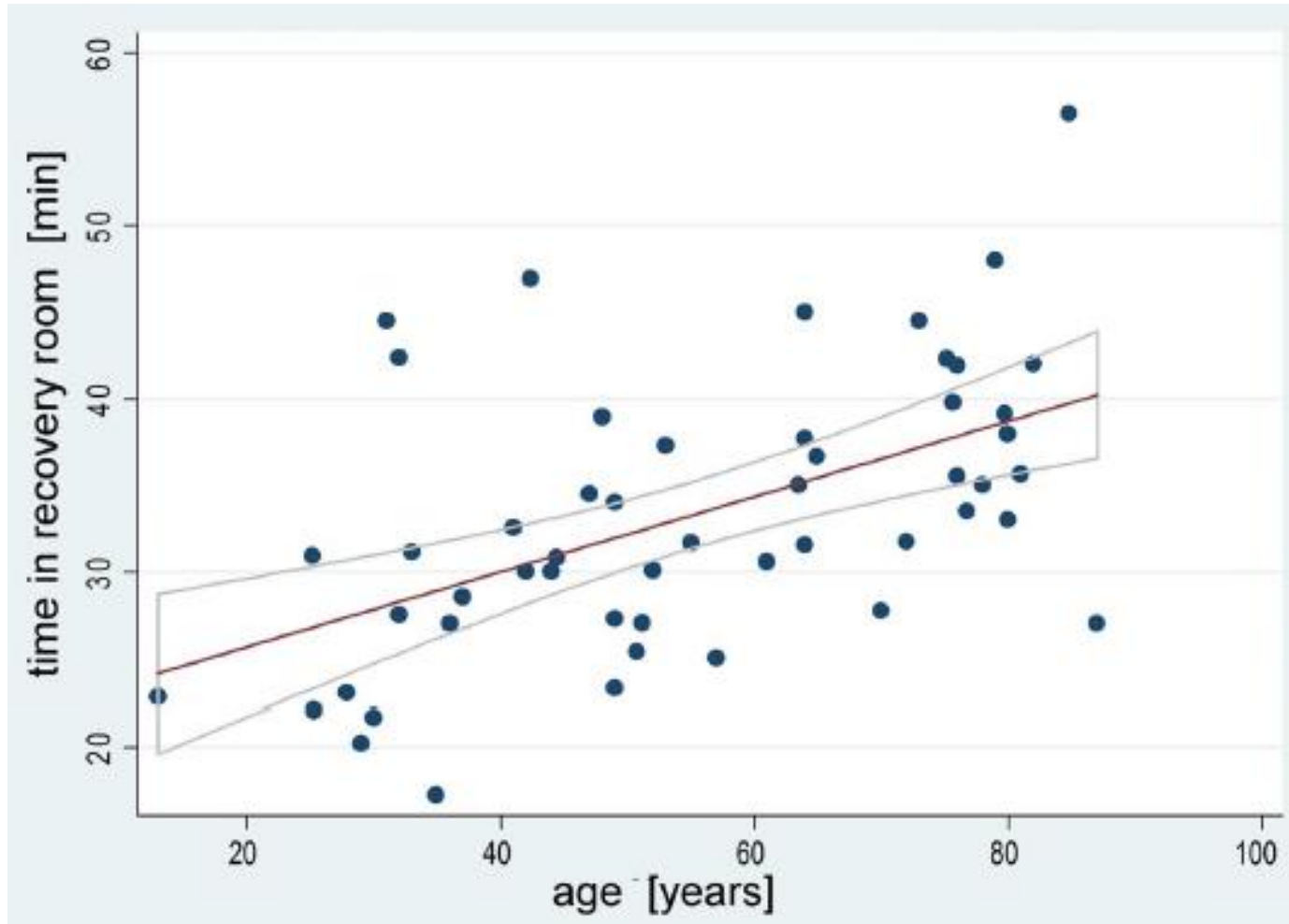
- lower the ST by flumazenil or caffeine if necessary
- be generous with hyperoxygenation
- use **ketamine** / etomidate if possible
- use **ketamine** / etomidate / remifentanyl as augmentation to propofol / barbiturates
- take enough time between start of propofol / barbiturates and stimulation (ASTI)
- take into account that ST can rise dramatically during ECT series – increase dose



- don't spare to much anesthesia dose – risk of PIA!
- don't spare to much charge - risk of underdosing / stimulation at or around ST

Problems

A widespread myth: Ketamine anesthesia - recovery room



No prolongation of time spent in recovery room by ketamine, but by age.

Sartorius A, Beuschlein J, Remennik D, Pfeifer AM, Karl S, Bumb JM, Aksay SS, Kranaster L, Janke C. Empirical ratio of the combined use of S-ketamine and propofol in electroconvulsive therapy and its impact on seizure quality. *Eur Arch Psychiatry Clin Neurosci.* 2021 Apr;271(3):457-463.

Problems

Ketamine anaesthesia: hypersalivation



risk factors:

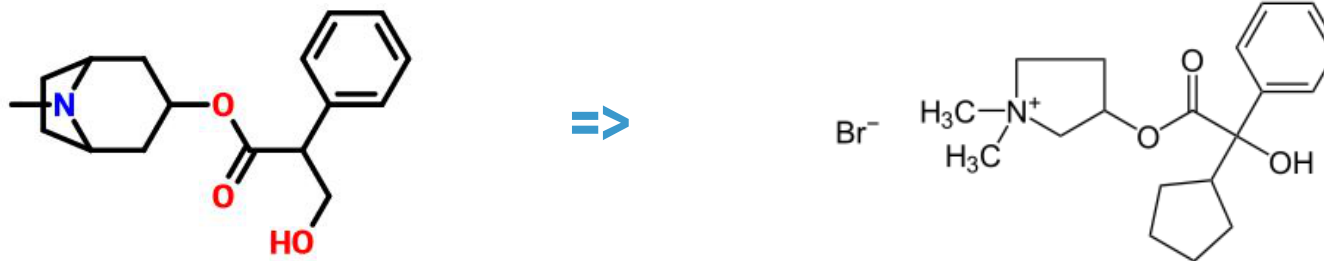
- smoking
- **ketamine**
- drugs like e.g. clozapine

- and:
parasympathetic stimulation

Problems

Ketamine anaesthesia - hypersalivation / sialorrhoe

- Former times: atropine, which is basically obsolete.
- Today: glycopyrrolate as a muscarinic receptor antagonist
- Both reduce hypersalivation (parasympatholytic)
- atropine **reduces** initial **bradycardia**, but increases ictal hypertension *

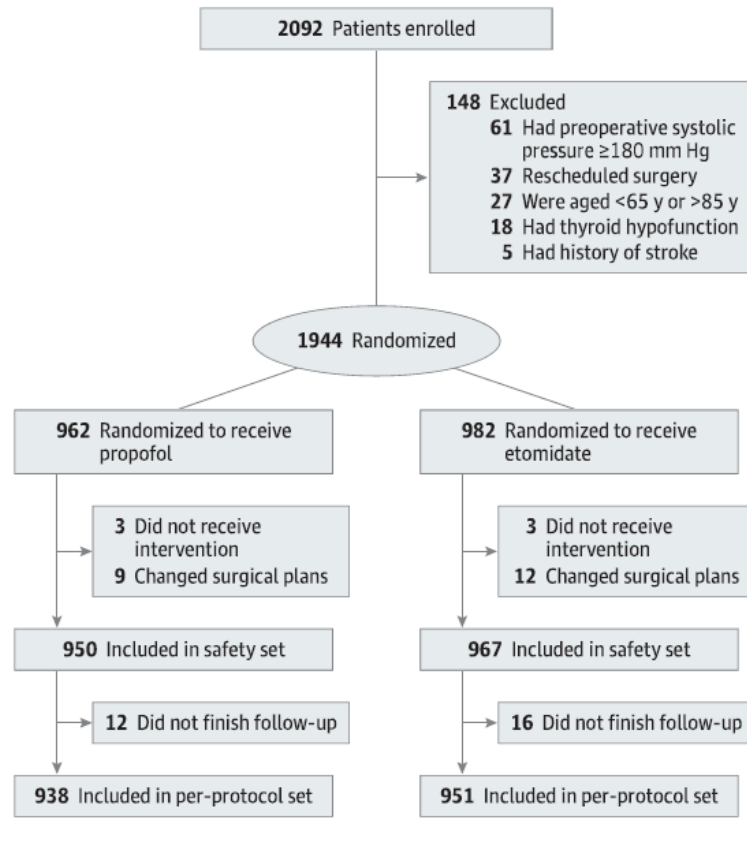


* Psychiatry Res. 2019 Jan;271:239-246
 Electro convulsive therapy: Modification of its
 effect on the autonomic nervous system using anti-
 cholinergic drugs.
 Christensen STJ, Staalsø JM, Jørgensen A, Weikop
 P, Olsen NV, Jørgensen MB.

Still an alternative : anaesthesia with etomidate



Figure 1. Patient Flowchart

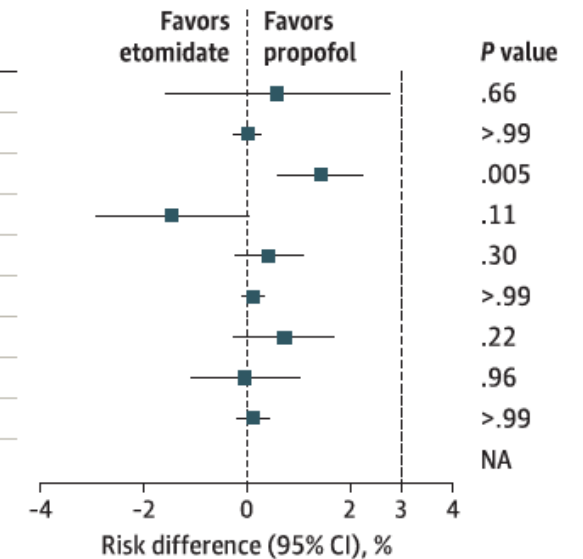


JAMA Surgery | **Original Investigation**

Effect of Etomidate vs Propofol for Total Intravenous Anesthesia on Major Postoperative Complications in Older Patients A Randomized Clinical Trial

Figure 2. In-Hospital Complications for Etomidate and Propofol Groups

Major in-hospital complications	No. %		Risk difference (95% CI)
	Etomidate group (n = 967)	Propofol group (n = 950)	
Total	90 (9.3)	83 (8.7)	0.6 (-1.6 to 2.7)
Cardiovascular	1 (0.1)	1 (0.1)	0 (-0.2 to 0.2)
Pulmonary	19 (2.0)	5 (0.5)	1.4 (0.6 to 2.3)
Gastrointestinal	32 (3.3)	45 (4.7)	-1.4 (-2.9 to 0.0)
Neurologic	9 (0.9)	5 (0.5)	0.4 (-0.2 to 1.0)
Urologic	1 (0.1)	0	0.1 (-0.1 to 0.3)
Infectious	19 (2.0)	12 (1.3)	0.7 (-0.2 to 1.6)
Hematologic	19 (2.0)	19 (2.0)	0.0 (-1.1 to 1.0)
Thrombosis	2 (0.2)	1 (0.1)	0.1 (-0.2 to 0.4)
Death	0	0	NA



Does Ketamine improve ECT ?

Yes, if you are NOT just adding a new substance (i.e. ketamine) and keep doses constant, but use solely ketamine OR ketamine plus a massively reduced other anesthetic (i.e. propofol):

- (maybe) better remission rates
- better depressive symptom reduction
- less charge needed and => less cognitive side effects !
- more hypersalivation, but no longer time needed in the recovery room

ECT is teamwork !



NACT Board (may 22nd):
Performing ECT
at a High-Quality Level
Is a Team Effort



**Elisabeth
Burgunder**



**Suna Su
Aksay**



Sebastian Karl



and:

Lana Said

Kent-Tjorben Böttcher

Gerrit Breitfelder

Sina Edinger

Christoph Janke

Eva Lamadé

Jessica Mächnich

Petra Mychajluk

Franziska Putschögl

Jonathan Reinwald

Moritz Spangemacher

Angela Zapp



**Laura
Kranaster**



**Jan Malte
Bumb**



Sina Edinger und Petra Mychajluk

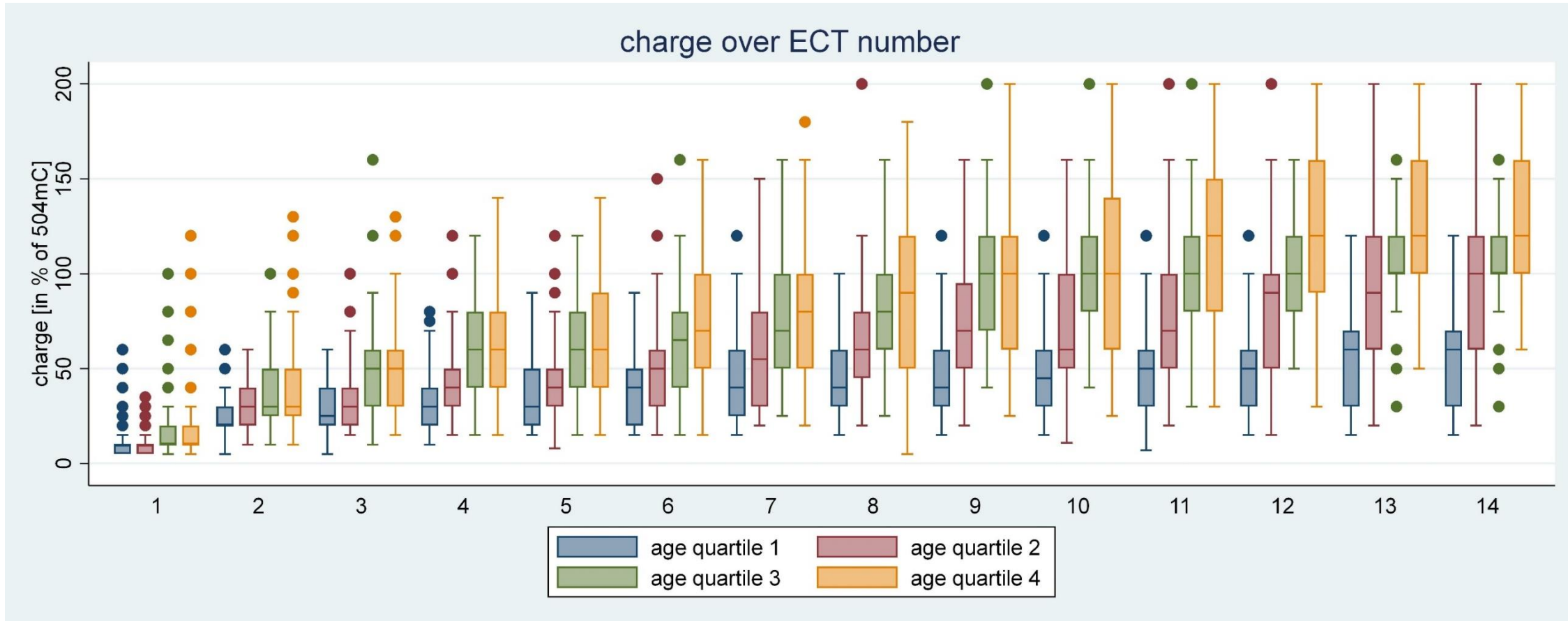


for your
attention

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Dose increase over ECT series is even faster with age



Interaction between age, ongoing ECT number [0 – 14] and stimulation dose [charge]

Division of age quartils: 1: < 42 years; 2: ≥ 42 years to 59 years; 3: ≥ 59 years to 73 years; 4: ≥ 73 years

Plempner J, Sartorius A, Karl S.

Age-Dependent Dose Increase During an Acute Electroconvulsive Therapy Series.

J ECT. 2023 Sep 1;39(3):193-196.

472 Patienten

4.871 EKTs

➔ in der Analyse