Jan-Otto Ottosson

Giacomo d'Elia

Lizzie Sand Strömgren

Dosing methods in ECT

Should the Scandinavian time-titration method be resumed?

NACT 16st Nordic Experience Meeting | Tallinn, May 25-27, 2022

Per Bergsholm, M.D., dr. med.

Psychiatrist, District General Hospital of Førde, Norway

NACT Nordic Association for Convulsive Therapy

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electroconvulsive

One day in 2018,
I sat in my home
in Førde,
Western Norway,
screening PubMed on
electroconvulsive.

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One day in 2018 I sat in my home in Førde, Western Norway, screening PubMed on electroconvulsive.

"Seizure threshold titration in electroconvulsive therapy is not a proven technique of dose optimization"

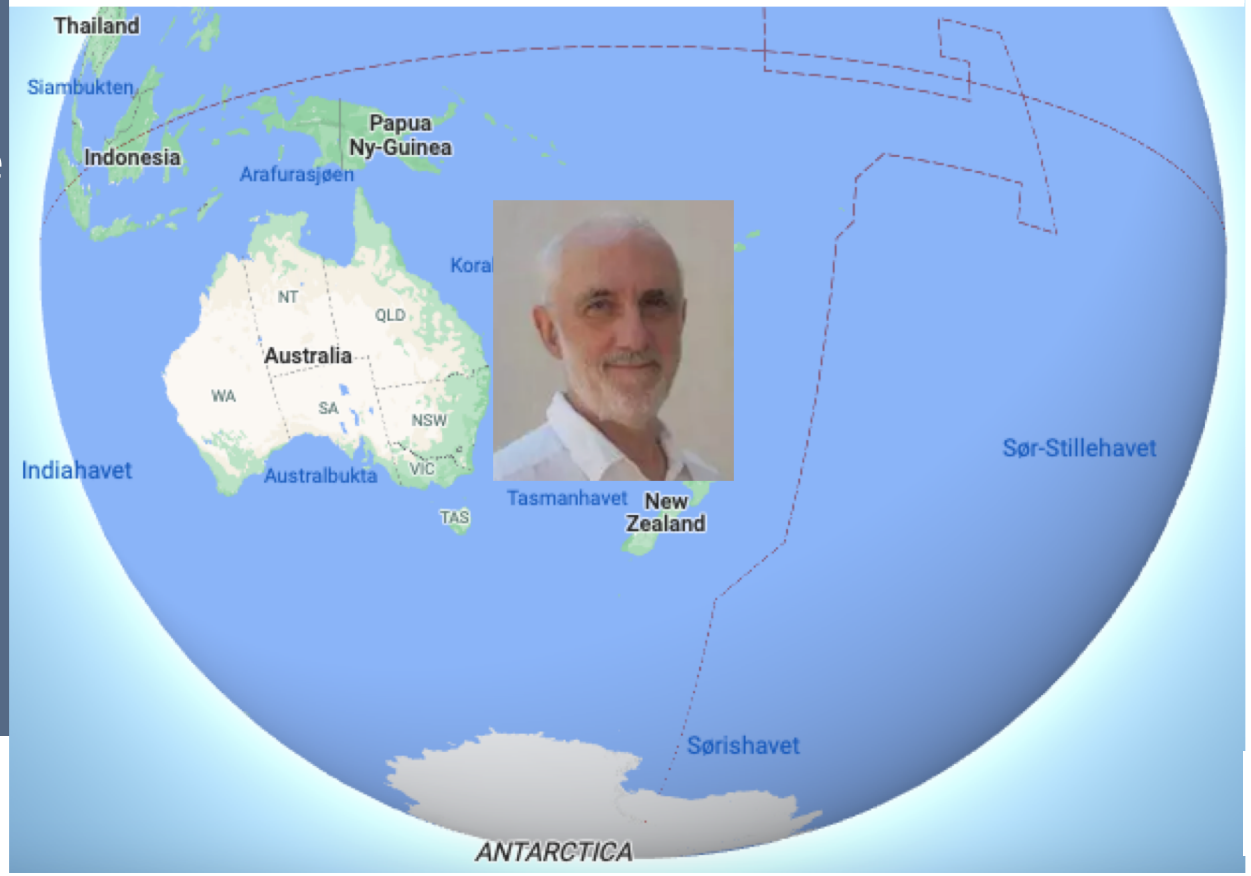
Viewpoint

Australian & New Zealand Journal of Psychiatry
2018, Vol. 52(5) 410–414

Electroconvulsive therapy stimulus titration: Not all it seems

Stephen J Rosenman

St John of God Health Services, Burwood
NSW, Australia



"It is a prematurely settled answer to an unsettled question that discourages further enquiry. It is an example of how practices, assumed scientific, enter medicine by obscure paths."

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Then an article from the other side of the world appeared. It was written by Stephen Rosenman in Australia. The title was "Electroconvulsive therapy stimulus titration: Not all it seems." He argued that "seizure threshold titration in electroconvulsive therapy is not a proven technique of dose optimization." Moreover, he wrote that "It is a prematurely settled answer to an unsettled question that discourages further enquiry. It is an example of how practices, assumed scientific, enter medicine by obscure paths."

ANZJP Correspondence
2018;52(7):711-712

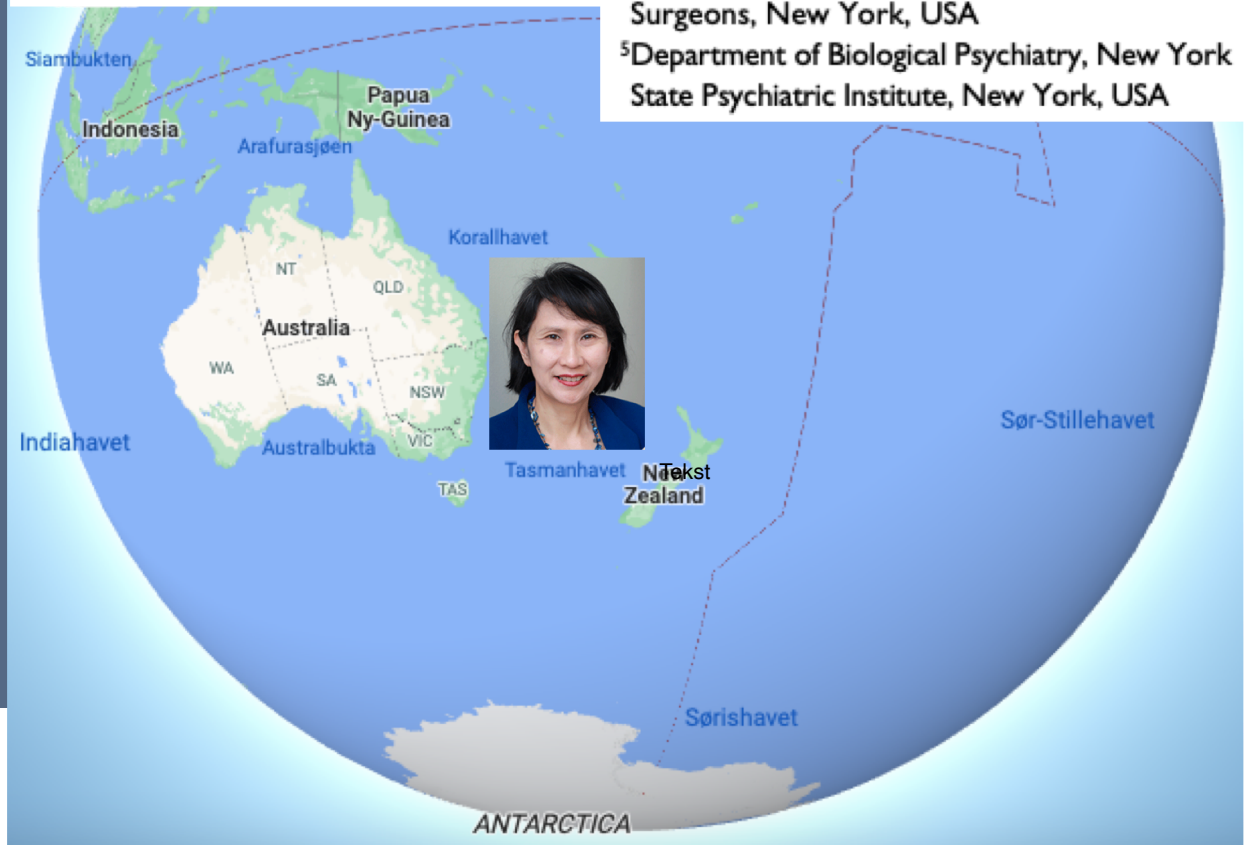
"we disagree with the conclusions he reached"

presenting thorough arguments against Rosenman

Response to Rosenman 'electroconvulsive therapy stimulus titration: Not all it seems'

Colleen K Loo[1,2], Donel Martin[1,2], William Vaughn McCall[3] and Harold Sackeim[4,5]

[1]School of Psychiatry, University of New South Wales, Sydney, NSW, Australia
[2]Black Dog Institute, University of New South Wales, Sydney, Australia
[3]Department Psychiatry and Health Behavior, Medical College of Georgia, Augusta University, Augusta, GA, USA
[4]Departments of Psychiatry and Radiology, Columbia University College of Physicians and Surgeons, New York, USA
[5]Department of Biological Psychiatry, New York State Psychiatric Institute, New York, USA



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In a commentary, Loo and Martin in Australia, together with McCall and Sackeim in USA, wrote that «we disagree with the conclusions he reached,» and they presented thorough arguments against Rosenman.

ANZJP Correspondence

2018;52(5):498-499

"We completely agree and believe this represents the field having rushed from small research datasets to premature implications in clinical practice."

The rush from bench to bedside in electroconvulsive therapy

Charles H Kellner and Elżbieta J Borys

New York Community Hospital, Brooklyn, NY, USA

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However, Kellner and Borys in New York commented that "we completely agree and believe this represents the field having rushed from small research datasets to premature implications in clinical practice."

Cronholm and Ottosson's threshold from the 1960s was a dynamic of *duration:*

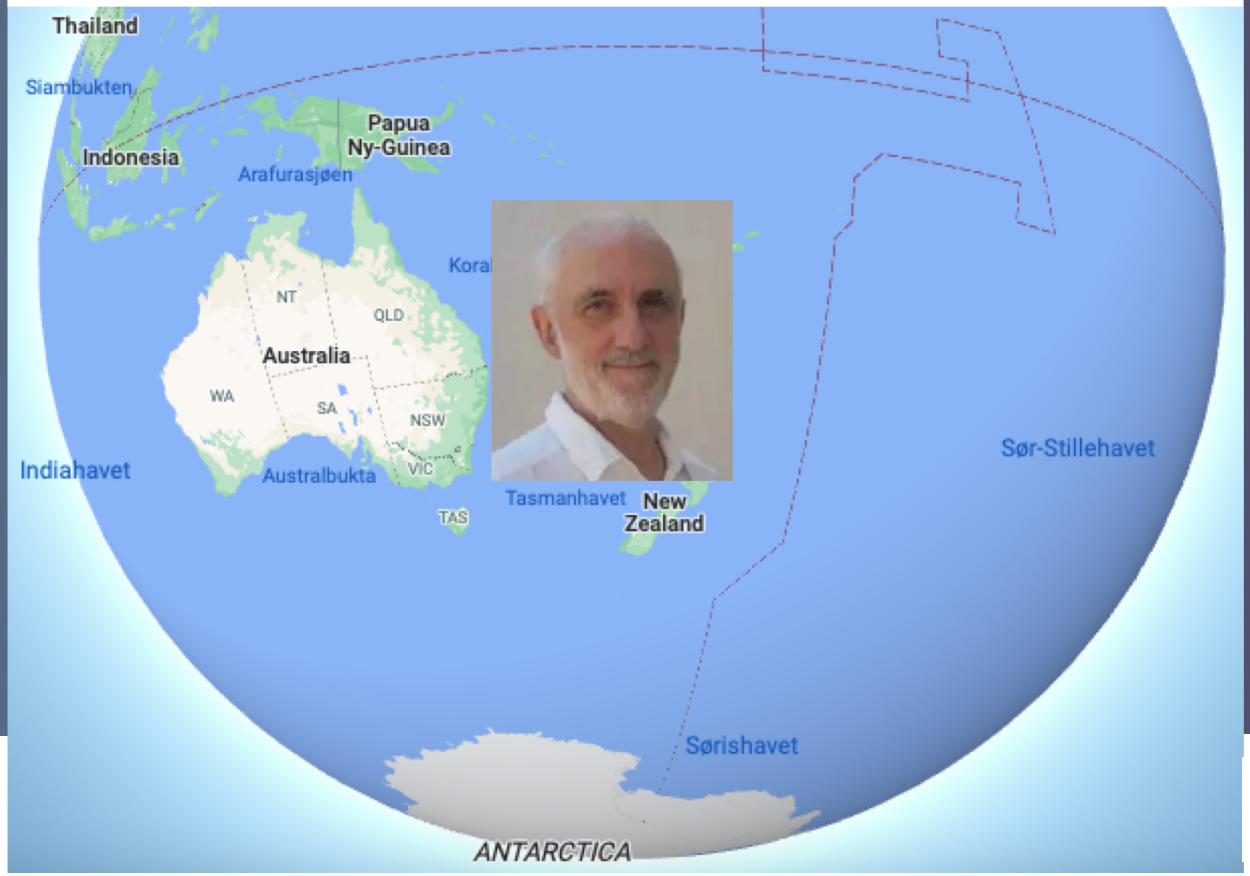
A stimulus long enough to *push* the evolving seizure far enough along its path that it reliably continues to completion

Viewpoint

Australian & New Zealand Journal of Psychiatry
2018, Vol. 52(5) 410–414

Electroconvulsive therapy stimulus titration: Not all it seems

Stephen J Rosenman



Sackeim's threshold from the 1980s is a dynamic of *intensity:*

A stimulus that would *trigger* the seizure by repeated stimuli with increasing frequency from 20 to 140 pulses per second

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Rosenman also wrote that Cronholm and Ottosson's threshold from the 1960s was a "dynamic of duration," i.e. a stimulus long enough to "push" the evolving seizure far enough along its path that it reliably continue to completion, whereas Sackeim's threshold from the1980s is a "dynamic of intensity," i.e. a stimulus that would "trigger" the seizure by repeated stimuli with increasing frequency from 20 to 140 pulses per second. Actually, it was Hertz in the original papers, so it should be 40 to 280 pps.

Now, my memory wandered backwards 40 years, to

Bergen

The most beautiful town in Norway

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Now, my memory wandered backwards 40 years, to Bergen, still Western Norway, where I lived and worked in the 1970s and 80s.

Origin of the Scandinavian time-titration dosing

Börje Cronholm (1913-83)
Stockholm

Jan-Otto Ottosson (1925-
Stockholm/Umeå/Göteborg
Bitemporal ECT

↓

Giacomo d'Elia (1934-)
Umeå, Sweden,
Bergen, Norway
Linköping, Sweden

Lizzie Sand Strömgren (1928-2007)
Aarhus, Denmark
Right Unilateral v Bitemporal ECT

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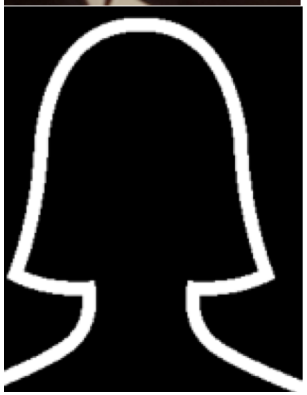
In 1979, I turned from neurology to psychiatry, and began working in the Psychiatric Clinic at Haukeland University Hospital. There I met professor Giacomo d'Elia, who had come from Sweden the year before, and to Sweden from Italy several years before. His supervisor in Sweden had been Jan-Otto Ottosson, who I also soon met. Giacomo became my supervisor. He taught me what I have named "the Scandinavian time-titration method."
Börje Cronholm and Jan-Otto Ottosson in Sweden, Giacomo d'Elia in Sweden and Norway, and Lizzie Sand Strömgren in Denmark, are the names behind this method.

Giacomo d'Elia 1934-

Jan-Otto Ottosson 1925-



Lizzie Sand Strömgren 1928-2007

The Scandinavian time-titration dosing

STIMULATION

1. Right unilateral parietotemporal with long distance (12 cm).
2. Not a prefixed stimulus duration
3. Current is interrupted as soon as the clonic contractions shift to the tonic phase, most readily observed in the plantar extension of the great toes

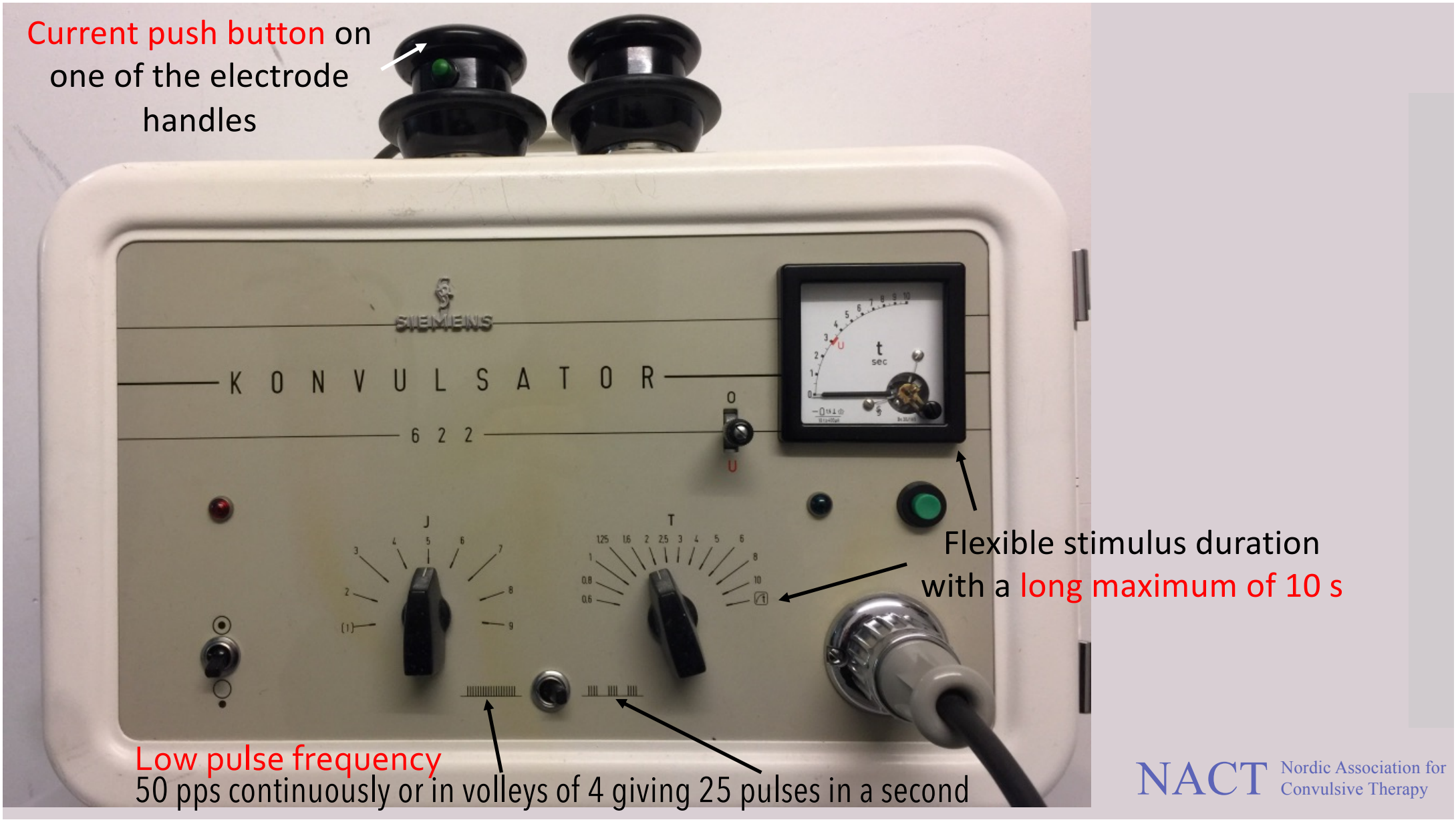
OBSERVATION AFTER STIMULATION

1. Maximum seizure activity usually ends by degrees, starting distally, and is succeeded by a comatose stage from which consciousness is gradually regained
2. The dissociative convulsion is followed by early awakening
3. The clonic form has no tonic phase, ends abruptly and simultaneously in the whole body, and lasts only 10 to 20 s. Both have lower antidepressant efficacy

d'Elia G, Ottosson J-O, Strömgren LS
Present Practice of Electroconvulsive Therapy in Scandinavia
Arch Gen Psychiatry 1983;40:577-81

NACT Nordic Association for Convulsive Therapy

In 1983 d'Elia, Ottosson and Sand Strömgren described this method in the Archives of General Psychiatry. It included
1. Right unilateral parietotemporal electrode placement with a long distance, at least 12 cm, between the center of the electrodes
2. Not a prefixed stimulus duration, and
3. Current is interrupted as soon as the clonic contractions shift to the tonic phase, which is most readily observed in the plantar extension of the great toes.



This technique was possible thanks to the Siemens Konvulsator, which had a flexible stimulus duration with a long maximum of 10 seconds, and a low pulse frequency of 50 pulses per second, continuously or in volleys of 4 giving 25 pulses in a second. It also had a current push button on one of its electrode handles.

Historical development of maximal pulse train duration in ECT devices in USA versus Scandinavia

2 s Mecta 1973 Blachely

3 s Mecta 1985

4 s Thymatron 1985

6 s Mecta 1997

8 s Thymatron 1990 Mecta 2003

Sackeim HA. Personal communication, Dec. 22, 2020

MECTA

Harold Sackeim (1951 -) New York

Thymatron

Richard Abrams (1929-2019) Illinois

Conrad Swartz (1946 -) Illinois/Oregon

Siemens Konvulsator

Börje Cronholm (1913-83) Stockholm

Jan-Otto Ottosson (1925 -) Stockholm-Umeå-Göteborg

10 s Siemens Konvulsator 1951, von Braunmühl

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However, the Konvulsator went out of production in the 1990s, and was replaced with MECTA and Thymatron from the USA. With the first versions of these devices the stimulus dose had to be preselected due to short maximum stimulus or pulse train duration. With the latest versions time-titration is possible. The Thymatron even has a program for intermittent pulse volleys, mimicking the Konvulsator. But time-titration has not been studied with these devices.

ANZJP Correspondence

2018;52:710–1.

"An alternative adequate and evidence-based dosing-strategy would be welcomed by the field."

"The only reasonable answer to the very valid questions raised by Rosenman is research and replication."

Time to replicate

Pascal Sienaert

Academic Center for ECT and Neuromodulation (AcCENT), University Psychiatric Center, KU Leuven, Kortenberg, Belgium

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A third commentary to Rosenman was by Pascal Sienaert in Leuven, Belgium. He wrote that "An alternative adequate and evidence-based dosing-strategy would be welcomed by the field." Especially, he called for replication studies in psychological sciences by writing that "the only reasonable answer to the very valid questions raised by Rosenman is research and replication."

The Scandinavian time-titration dosing may be an adequate, evidence-based alternative, which has been replicated:

Right unilateral ECT is highly efficacious and equal to bitemporal ECT, with less cognitive side effects.

Randomized controlled trials

1. d'Elia D. Unilateral electroconvulsive therapy
   Acta Psychiatr Scand Suppl 1970;215:1-98

2. Sand Strömgren L. Unilateral versus bilateral electroconvulsive therapy. Investigations into the therapeutic effect in endogenous depression
   Acta Psychiatr Scand Suppl 1973;240:1-65
   Fromholt P, Christensen AL, Strömgren LS. The effects of unilateral and bilateral electroconvulsive therapy on memory
   Acta Psychiatr Scand 1973;49:466-78

3. Lamy S, Bergsholm P, d'Elia G. The antidepressant efficacy of high-dose nondominant long-distance parietotemporal and bitemporal electroconvulsive therapy. *Convuls Ther 1994;10:43-52*

Patient series

4. Strömgren LS. Is bilateral ECT ever indicated?
   Acta Psychiatr Scand 1984;69:484-90

5. Strömgren LS. Electroconvulsive Therapy in Aarhus, Denmark, in 1984: Its Application in nondepressive disorders. *Convuls Ther 1988;4:306-13*

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Actually, the Scandinavian time-titration dosing may be an adequate, evidence-based alternative. It has been replicated a lot of times, first by Cronholm and Ottosson with bitemporal ECT, not shown here, then by demonstrating right unilateral ECT to be highly efficacious and equal to bitemporal ECT, with less cognitive side effects. There are three randomized controlled studies, and two naturalistic studies. Especially, the study number 4 is still exceptional in its kind.

Acute Psychiatric Department, Oslo University Hospital at Ullevål

In 1912 to 15 I worked in the Acute Psychiatric Department of Oslo University Hospital, at Ullevål. Or

Postictal Reorientation Time (PRT)

Diakonhjemmet Hospital, Department of Geriatric Psychiatry, Oslo

- Longer PRTs at the first and third treatments predicted a more rapid decline and a lower end-point in continuous $HRSD_{17}$ scores
- None of the patients who recovered from disorientation in less than 5 min met the remission criterion
- All patients with PRTs of 35 min or more achieved remission after 12 treatments or less

Tor Magne Bjølseth et al. Speed of recovery from disorientation may predict the treatment outcome of electroconvulsive therapy (ECT) in elderly patients with major depression. *J Affective Disord 2016;190:178-86*

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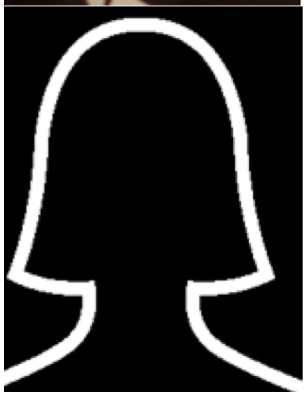
He had found that longer postictal reorientation time, PRT, (measured from the resumption of spontaneous respiration and eye opening), at the first and third treatments predicted a more rapid decline and a lower end-point in continuous Hamilton scores. None of the patients who recovered from disorientation in less than 5 minutes met the remission criterion, whereas all with PRTs of 35 minutes or more achieved remission after 12 treatments or less.

Giacomo d'Elia
1934-

Jan-Otto Ottosson
1925-



Lizzie Sand Strömgren
1928-2007

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d'Elia G, Ottosson J-O, Strömgren LS
Present Practice of Electroconvulsive Therapy in Scandinavia
Arch Gen Psychiatry 1983;40:577-81

NACT Nordic Association for Convulsive Therapy

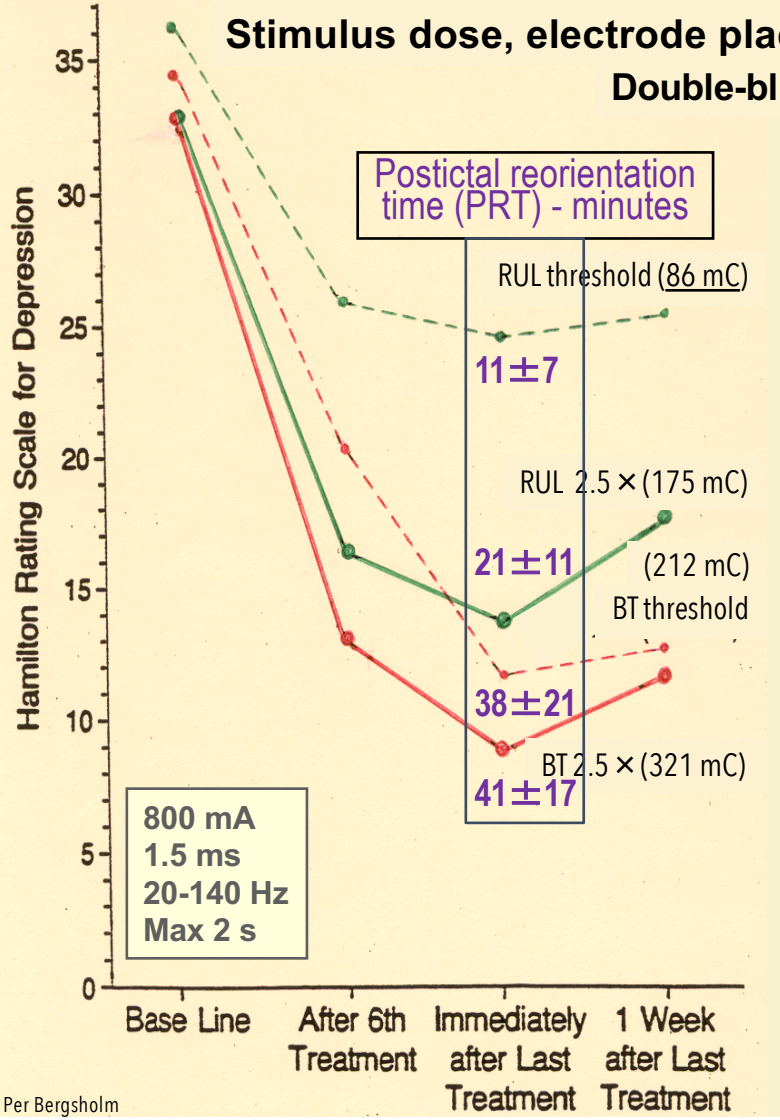
We found that this fits with d'Elia, Ottosson and Strömgren's inclusion of a postictal comatose stage in their description of maximum seizure activity, whereas early awakening is one of the signs of insufficient seizure activity, as is pure clonic convulsions.

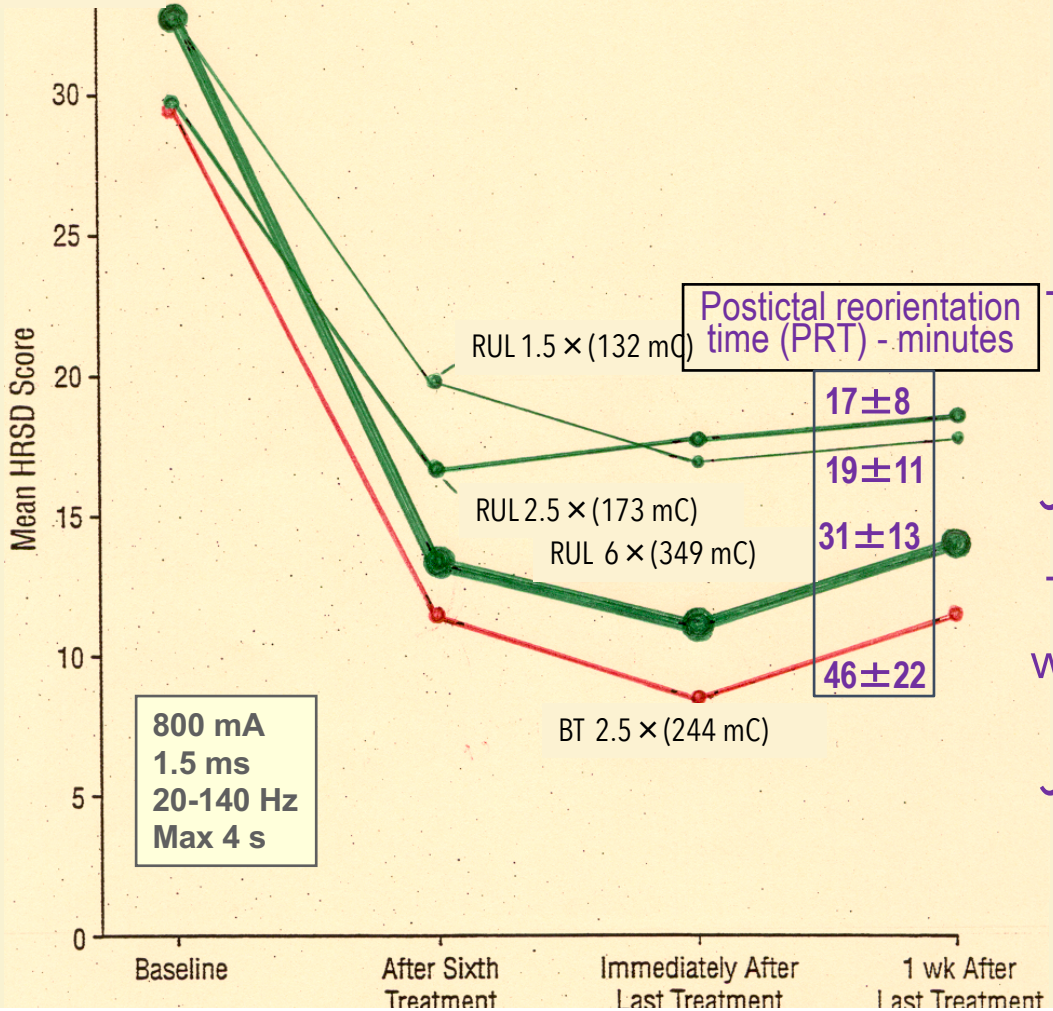
EFFECTS OF STIMULUS INTENSITY AND ELECTRODE PLACEMENT ON THE EFFICACY AND COGNITIVE EFFECTS OF ELECTROCONVULSIVE THERAPY. Sackeim HA et al. N Engl J Med 1993;328:839-46.

A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND COMPARISON OF BILATERAL AND RIGHT UNILATERAL ELECTROCONVULSIVE THERAPY AT DIFFERENT STIMULUS INTENSITIES. Sackeim HA et al. Arch Gen Psychiatry 2000;57:425-34.

Stimulus dose, electrode placement and PRT versus response

Double-blind RCTs





Per Bergsholm

PRT

The groups with best outcome:

~30-45 min

The groups with poorest outcome:

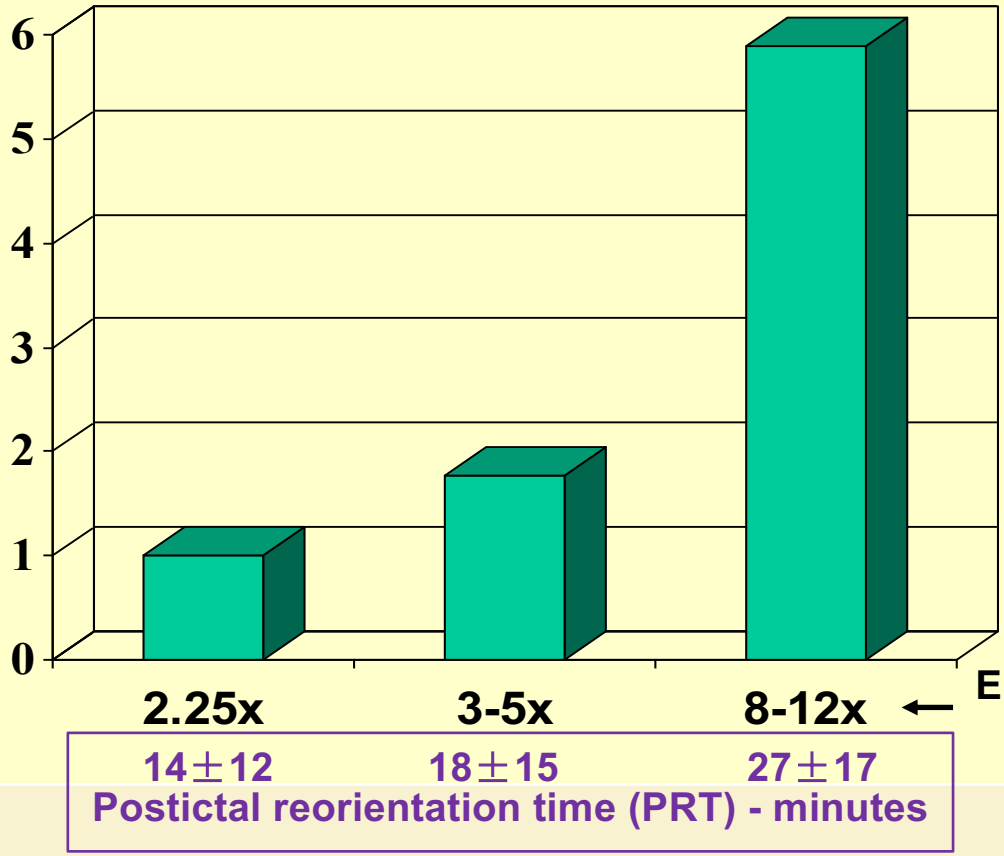
~10-20 min

It also fits with studies by Sackeim and coworkers using brief 1.5 ms pulses, published in 1993 and 2000. The patient groups with best outcome had PRTs of 30 to 45 minutes, the groups with poorest outcome 10 to 20 minutes.

TITRATED MODERATELY SUPRATHRESHOLD VS FIXED HIGH-DOSE RIGHT UNILATERAL ELECTROCONVULSIVE THERAPY

Willian Vaughn McCall, DM Reboussin, RD Weiner, HA Sackeim

Arch Gen Psychiatry 2000;57:438-44



PRT

The group with best outcome: **~30 min**

The groups with poorest outcome: **~15-20 min**

Moreover, in this study by McCall and coworkers, including Sackeim, also published in 2000, PRT was about 30 minutes in the best outcome group, versus 15 to 20 minutes in the poorest outcome groups.

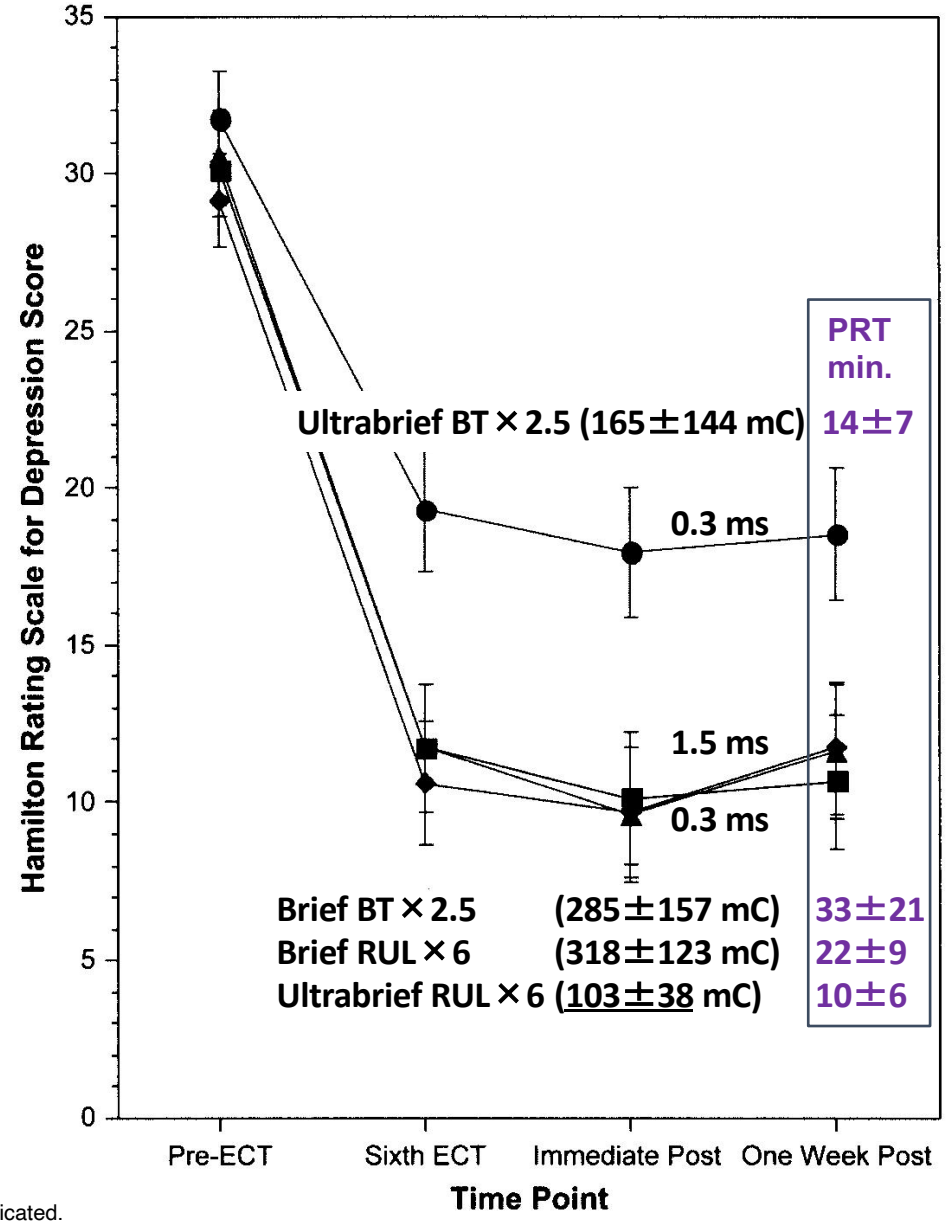
Stimulus dose, pulse width, electrode placement and PRT versus response

Double-blind RCT

Sackeim HA et al (NY)

Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy

Brain Stimulation 2008;1:71-83,



The groups with good outcome:
BT&RUL 1.5 ms
~20-30 min
RUL 0.3 ms
~10 min

The group with poor outcome:
BT 0.25 ms
~15 min

This study, published by the Sackeim-group in 2008, is more complicated.
Using ULTRABRIEF pulses in right UNILATERAL ECT with 6 times threshold dose, outcome was good with a mean PRT of only 10 minutes. This deviates from the three studies they published in 1993 and 2000. However, there may have been something unusual with this group of patients, because mean threshold was exceptionally low, resulting in a mean dose of only 103 mC. In similar studies I have seen, mean dose has been 2 to 5 times higher.
Using ultrabrief pulses in BITEMPORAL ECT, with 2.5 times threshold dose, outcome was poor, mean PRT 14 minutes and mean dose165 mC. This is consistent with the three previous studies.
Using BRIEF 1.5 ms pulses outcome was good with BOTH bitemporal and right unilateral ECT. With bitemporal ECT PRT was 33 minutes and dose 285 mC. With right unilateral ECT PRT was 22 minutes and dose 318 mC. This, too, is consistent with the previous studies.

Five dosing methods in ECT

1. **Time-titration dosing** Cronholm, Ottosson, d'Elia, Sand Strömgren 1957-94

2. **Fixed high dosing: 50-100 % of maximal output** Tradition of unknown origin

3. **Formula/age-based dosing**
   Full-Age dosing: 5 x age mC for RUL ECT Abrams & Swartz 1985
   BF ECT closer to Full-Age than Half-Age dosing Bjølseth et al 2016

   Half-Age dosing: 2.5 x age mC for BT ECT Petrides & Fink 1996
   Optionally ± 5-10 % (?) for male/female gender

4. **Seizure threshold-based dosing**
   RUL ECT (2½)-5-8 x ST, BT ECT 1.5-2.5 x ST Sackeim, McCall 1987-2009

5. **Benchmark dosing: Adjusting dose at each session to an initial optimal benchmark** Swartz 1994-2009

Bergsholm P, Bjølseth TM. Dosing methods in electroconvulsive therapy: should the Scandinavian time-titration method be resumed? *Nord J Psychiatry 2021 Aug 1, 1-7*

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These are the five dosing methods in ECT:
1. The Scandinavian time-titration dosing
2. Fixed high dosing, i.e. 50 to 100 % of the device's maximal output. Occasionally a lower dose has been used.
3. Formula- or age-based dosing, i.e. Full-Age dosing of 5 times age mC for RUL ECT, close to this for BF ECT, and Half-Age dosing of 2.5 times age mC for BT ECT.
4. Seizure threshold-based dosing, i.e. for RUL ECT 2½ to 8 times threshold dose, for BT ECT 1.5 to 2.5 times threshold dose.
5. Benchmark dosing, i.e. the dose is adjusted at each session to an initial optimal benchmark, based on satisfactory peak heart rate and tonic convulsions.

National guidelines prefering threshold titration

- American Psychiatric Association *The Practice of Electroconvulsive Therapy, 2001 pp 158-9*
  Threshold and Formula/Age > Fixed high-dose for special situations.
  «empirical titration provides the most precise method» RUL 2.5-6 x ST. BT 1.5-2.5 x ST
- Canadian Network for Mood and Anxiety Treatment (CANMAT) *Can J Psychiatry 2016;61:561-75*
  Threshold only. First line: brief RUL 5-6 x ST, brief BF 1.5-2.0 x ST
  Second line: ultrabrief RUL up to 8 x ST, ultrabrief BF 1.5-2.0 x ST, brief BT 1.5-2.0 x ST
- Royal College of Psychiatrists, UK & Ireland *The ECT Handbook, 2019 pp 183-201*
  Threshold > Age. «measurements of the ST has real advantages». RUL 6 x ST. BT 1.5 x ST
- Royal Australian and New Zealand College of Psychiatrists *ANZJP 2019;53:609-23*
  Threshold > Age. «It is recommended that the stimulus is determined on an individual basis using the dose titration method.»

RUL	0.3 ms: 6 x ST	–	0.5-1.0 ms:	5-6	x ST
BF&BT	1.0 ms: 1.5 x ST	–	0.5 ms:	1.5-2.5	x ST

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National guidelines from USA, Canada, UK & Ireland, and Australia & New Zealand favor seizure threshold based dosing. The CANMAT even mentions threshold based dosing only.

Critique of seizure threshold based dosing

Conrad M Swartz. «A fixed multiple does not have similar effects with different patients - It does not account for common highly variable and large changes of seizure threshold along the course - Patients who respond to low stimulus doses are not selected to receive them; nor are patients who require high doses» (J ECT 2001;17:87–90).

Charles H Kellner. «the distribution of threshold values is tightly clustered in the 10–40% range, with a few outliers accounting for the large range. Thus, for most patients dose titration is unnecessary. For average practitioners, dose titration is cumbersome; for patients, it may lead to increased side effects at the first treatment session.» *«The modal ECT treatment»:* RUL 75% – BF 50% – BT 30-60% (J ECT 2001;17:1–2).

Richard Abrams. «the seizure threshold is a 'mooving target' that varies with the stimulus parameters … an infinite variety of seizure thresholds exist in the same patient, with no rationale provided for choosing among them.» *«The best chance of success»:* RUL 100% – BF age – BT half-age, «with no demonstrated long-term or persistent side effects» (J ECT 2002;18:3–9,14-5).

Max Fink. «Seizure threshold determinations to determine electricity dosing are neither necessary nor useful for effective ECT - unnecessarily reduces the efficiency of the treatment course.» (Acta Psychiatr Scand 2014;129: 417–26).

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However, these guidelines stand in contrast to critique from these outstanding ECT specialists. Here are some excerps from their writings.

Critique of seizure threshold based dosing

The essentials of this critique are that

1) a fixed multiply does not have similar effects with different patients,
2) the threshold changes along the course in half of the patients,

3) the threshold varies with the stimulus parameters in the same patient,
4) In the clinic, threshold titration is cumbersome, increases side effects, reduces efficiency, and is neither necessary nor useful.

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The essentials of this critique are that
1) a fixed multiply does not have similar effects with different patients,
2) the threshold changes along the treatment course in half of the patients,
3) the threshold varies with the stimulus parameters in the same patient, and
4) in the clinic, threshold titration is cumbersome, increases side effects, reduces efficiency, and is neither necessary nor useful.

Scandinavian national guidelines are without preferences

- The Danish Psychiatric Society *ECT-vejledning, 2020 p 47*
  Age = Threshold
  BT at least 1.5 x ST, RUL at least 2.5 x ST
- The Swedish Psychiatric Association *Kliniska riktlinjer för ECT, 2014 pp 51-2*
  Age = Threshold. «The initial setting is most often done according to age and gender, from tables offered by the manufactors of the ECT devices»
- Norwegian Health Directory *Nasjonal faglig retningslinje om bruk av ECT, 2017 p 63*
  «Strong recommendation» (0.5 ms pulses):
  Age = Threshold RUL 5-6 x ST, BT about half the doses of RUL
  «Moderate recommendation»: BF (0.5 ms pulses): About half the doses of RUL

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Scandinavian national guidelines equate age- and threshold-based dosings.

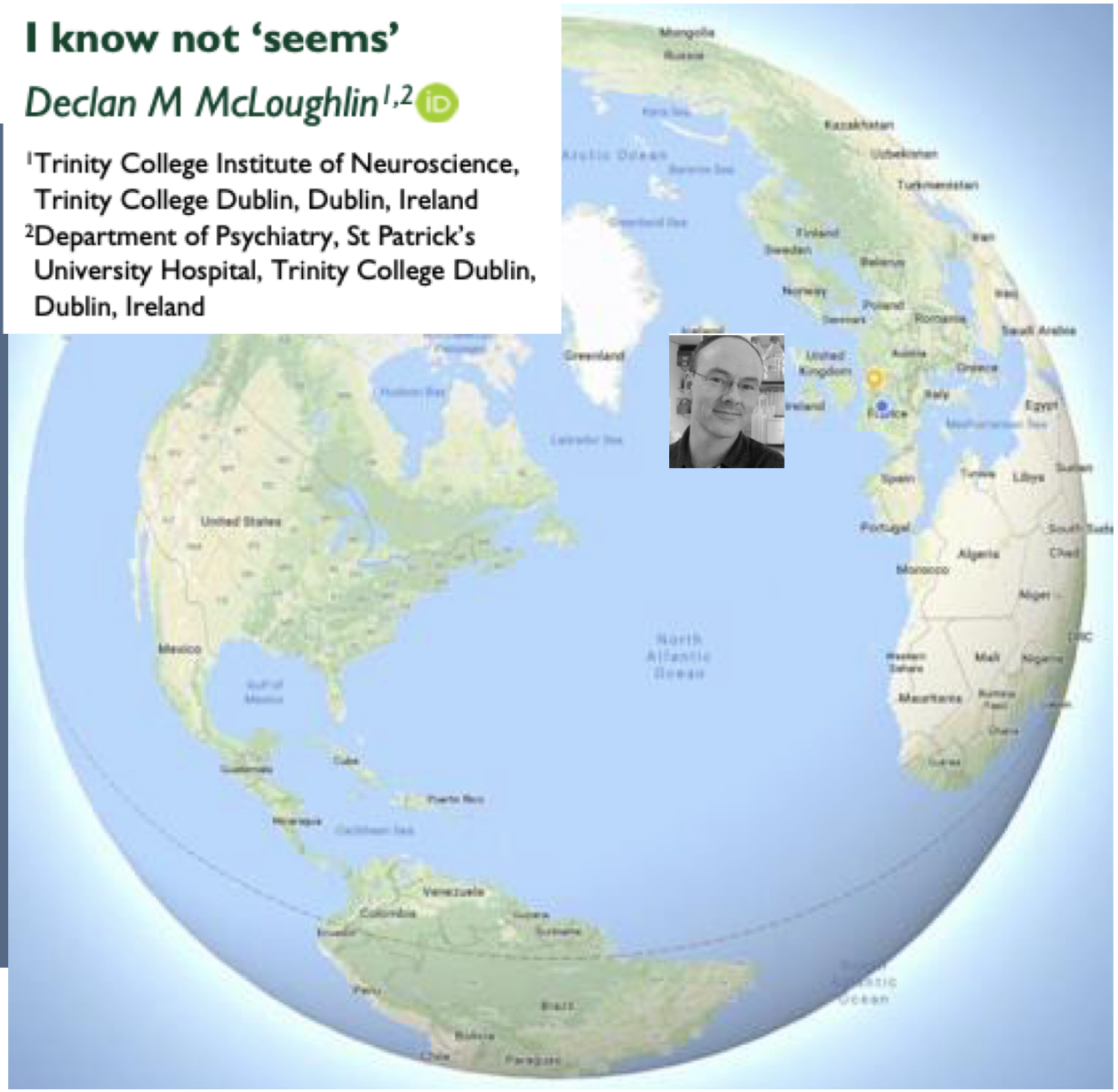
ANZJP Correspondence
2018;52(7):709-710

"the best way to administer ECT with regard to optimizing therapeutic benefit and simultaneously minimizing cognitive side-effects is not known."

I know not 'seems'

Declan M McLoughlin[1,2]

[1]Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
[2]Department of Psychiatry, St Patrick's University Hospital, Trinity College Dublin, Dublin, Ireland



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A fourth comment to Rosenman came from Declan McLoughlin in Dublin. He wrote that "The best way to administer ECT with regard to optimizing therapeutic benefit and simultaneously minimizing cognitive side-effects is not known."

Psychiatry Research
294 (2020) 113497

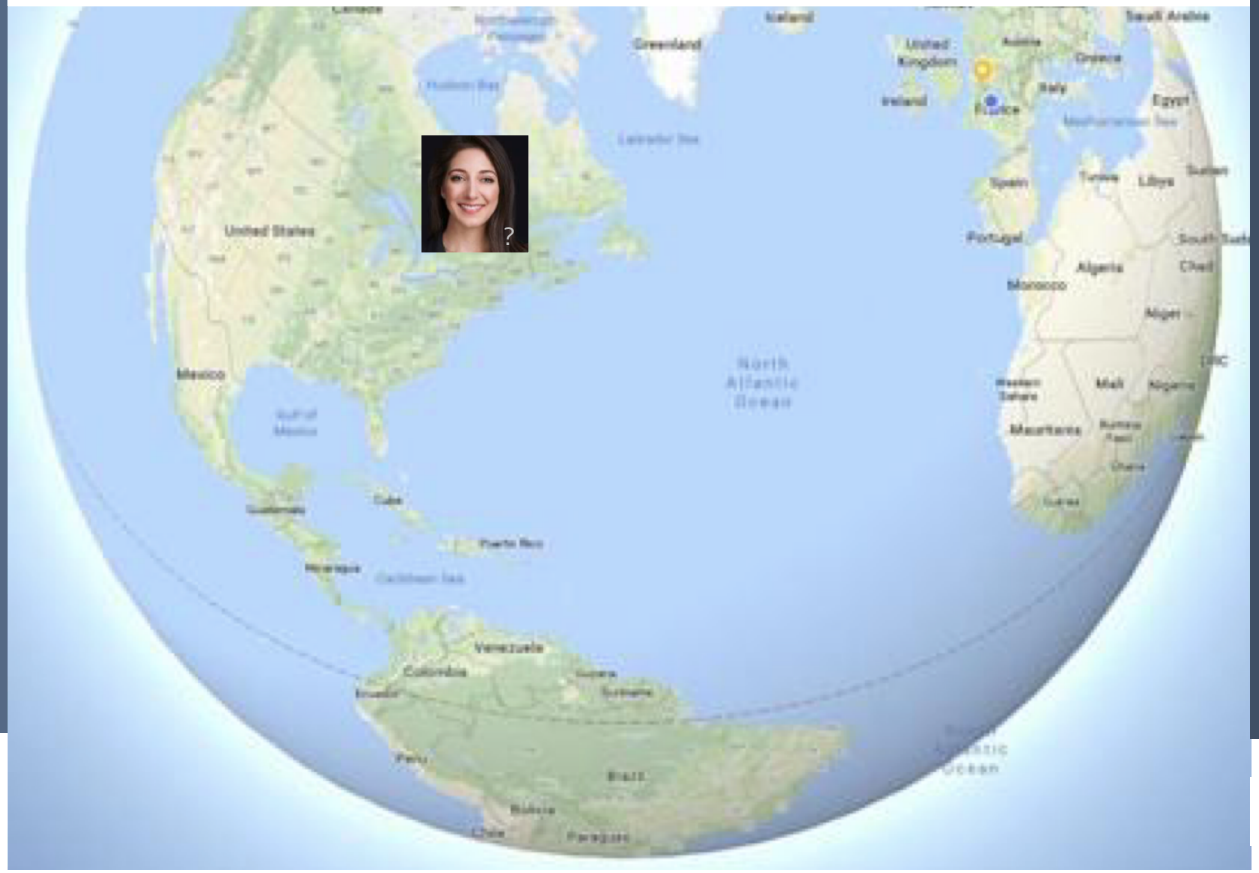
"No clear recommend-ations could be drawn regarding the clinical superiority of one method."

Review article

The clinical relevance of dose titration in electroconvulsive therapy: A systematic review of the literature

Marilyne Landry[a,1], Simon Lafrenière[a,1,*], Simon Patry[a,b,c], Stéphane Potvin[a,c], Morgane Lemasson[a,b,c]

[a] Département de psychiatrie et d'addictologie, Université de Montréal, Montréal, Québec, Canada
[b] Centre d'excellence en électroconvulsivothérapie du Québec (CEECTQ), CIUSSS de l'Est-de-l'Île-de-Montréal, Montréal, Québec, Canada
[c] Centre de recherche de l'Institut Universitaire en Santé Mentale de Montréal (IUSMM), CIUSSS de l'Est-de-l'Île-de-Montréal, Montréal, Québec, Canada



7 articles with clinical comparisons of Multiple threshold with Fixed or Age-based dosing:

2 RCTs v Fixed (n=19 & 36)
2 retrospective v Fixed (n=34 & 46)
2 retrospective v Age-based (n=22 & 69)
1 comparative cohort v Age-based (n= 79)

14 articles with hypo-thetical comparisons of Multiple threshold with Fixed and Age-based dosing

Two years later this was supported by Marilyne Landry and coworkers in Montréal. They published a systematic review of the clinical relevance of the seizure threshold-based method compared to the age- and fixed dose methods. They concluded that "no clear recommendations could be drawn regarding the clinical superiority of one method."
[However, there was a certain trend in favor of dose titration as three out of seven articles with clinical comparisons and eight out of 14 articles depicting hypothetical comparisons tended to favor dose titration, mostly in order to reduce the risk of over- and underdosing.]

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REVIEW ARTICLE

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Dosing methods in electroconvulsive therapy: should the Scandinavian time-titration method be resumed?

Per Bergsholm[a] and Tor Magne Bjølseth[b]

[a]Department of Psychiatry, District General Hospital of Førde, ISP, Sogndal, Norway; [b]Diakonhjemmet Hospital, Department of Geriatric Psychiatry, Oslo, Norway

Our recommendation is that the Scandinavian time-titration method should be resumed and tested against other methods. It may have advantages as an individualized method. It may have been prematurely abandoned, due to technical reasons.

NACT Nordic Association for Convulsive Therapy

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In time-titration the current is continued beyond the seizure threshold until generalized tonic contractions have developed. As this is done in every session, it allows for an often rising seizure threshold during the treatment course.

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The centerpiece of time-titration is a low number of pulses each second and a flexible duration of the pulse train.
In the Scandinavian studies pulse train duration was 1.8 to 10 s, mostly less than 8 s. But the number of pulses delivered was only 45 to 250, due to only 25 pulses in a second delivered in separate volleys with a frequency of 50 pps inside each volley.
I think the risk of overdosing is low. The risk may be higher of underdosing by interrupting the stimulus too early.

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A sufficiently long postictal reorientation time, PRT,* may be the ultimate sign of a therapeutic seizure. However, the optimal PRT is not known. It may be somewhat between 5 and 30 minutes, from the resumption of spontaneous respiration and eye opening, and it may depend on age.

*Also denoted Time to Recover Orientation (TRO)

NACT Nordic Association for Convulsive Therapy

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CONCLUSION

The clincal indicators of an effective stimulation are 1) generalized tonic contractions, and 2) a postictal disorientation phase. These may be better indicators than age and seizure threshold.
The observation of when tonic contractions are generalized is somewhat arbitrary. However, so is the determination of seizure threshold and the number this is to be multiplied with.

NACT Nordic Association for Convulsive Therapy

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1) generalized tonic contractions, and 2) a postical disorientation phase. These may be better indicators than age and seizure threshold.
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EDITORIAL

Dosing methods in electroconvulsive therapy (ECT): towards the modal ECT technique

Thanks to Charles and Martin for their inspiring and to-the-point commentaries ☺

Charles H. Kellner
Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, USA

Martin B. Jørgensen
Psychiatric Centre Copenhagen, Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

NACT Nordic Association for Convulsive Therapy

Finally, thanks to Charles and Martin for their kind and thougtful editorial comments to our article in Nordic Journal of Psychiatry.

ADDENDUM

Then a surprise – an addendum. I presented the foregoing lecture for the first time on April 23 at the ISEN, i.e. the International Society for ECT and Neurostimulation. A few hours later I got an e-mail from Max Fink.

Max Fink

Flurothyl seizures

Til: Per Bergsholm

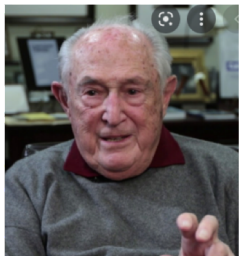
23. april 2022 kl. 23:13

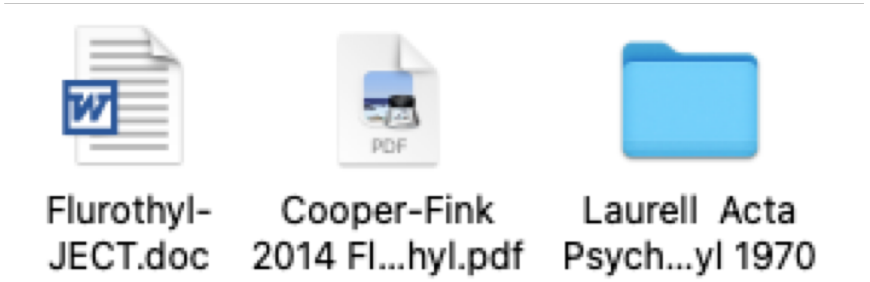
Dear Dr Bergsholm,

Your presentation at ISEN today was an effort to revive more effective dosing methods than the widely used and often ineffective threshold dosing. In the 1960s, Jan-Otto Ottosson and I tested flurothyl induced seizures. While the technic was effective, our inability to have full anesthesia air management ended our interest. In 2014 I attempted to recall flurothyl. My recollection and the work of William Karliner stimulate me to reconsider its testing. At age 99, I no longer have the opportunity.

The degradation of ECT as a neuromodulation, the widespread use of inadequate dosing methods has led to widespread inadequate treatments. Perhaps, with your skills, you may revive flurothyl seizures. Best of luck in your research.

Max Fink, M.D.





He wrote: Your presentation at ISEN today was an effort to revive more effective dosing methods than the widely used and often ineffective threshold dosing. In the 1960s, Jan-Otto Ottosson and I tested flurothyl induced seizures. While the technic was effective, our inability to have full anesthesia air management ended our interest. In 2014 I attempted to recall flurothyl. My recollection and the work of William Karliner stimulate me to reconsider its testing. At age 99, I no longer have the opportunity.
The degradation of ECT as a neuromodulation, the widespread use of inadequate dosing methods has led to widespread inadequate treatments. Perhaps, with your skills, you may revive flurothyl seizures. Best of luck in your research. Max Fink. - He has three attachments.

Kathryn COOPER | Post-doctor...
researchgate.net

The Chemical Induction of Seizures in Psychiatric Therapy

Were Flurothyl (Indoklon) and Pentylenetetrazol (Metrazol) Abandoned Prematurely?

Kathryn Cooper, BS and Max Fink, MD†‡*

Background: Camphor-induced and pentylenetetrazol-induced brain seizures were first used to relieve psychiatric illnesses in 1934. Electrical inductions (electroconvulsive therapy, ECT) followed in 1938. These were easier and less expensive to administer and quickly became the main treatment method. In 1957, seizure induction with the inhalant anesthetic flurothyl was tested and found to be clinically effective.

For many decades, complaints of memory loss have stigmatized and inhibited ECT use. Many variations of electricity in form, electrode placement, dosing, and stimulation method offered some relief, but complaints still limit its use.

Methods: The experience with chemical inductions of seizures was reviewed based on searches for reports of each agent in Medline and in the archival files of original studies by the early investigators.

Findings: Camphor injections were inefficient and were rapidly replaced by pentylenetetrazol. These were effective but difficult to administer. Flurothyl inhalation–induced seizures were as clinically effective as electrical inductions with lesser effects on memory functions. Flurothyl inductions were discarded because of the persistence of the ethereal aroma and the fears induced in the professional staff that they might seize.

Conclusions: Persistent complaints of memory loss plague electricity induced seizures. Flurothyl induced seizures are clinically as effective without the memory effects associated with electricity. Reexamination of seizure inductions using flurothyl in modern anesthesia facilities is encouraged to relieve medication-resistant patients with mood disorders and catatonia.

Key Words: electroconvulsive therapy, pentylenetetrazol, flurothyl, seizures, history

(*J Clin Psychopharmacol* 2014;34: 00–00)

The first experiments inducing brain seizures in patients with psychiatric illness were conducted by the Hungarian neuropathologist Ladislas Meduna. When he found deficits in the numbers of glial cells in the brains of patients with schizophrenia and a surplus among those with epilepsy, he conceived of an antagonism between schizophrenia and epilepsy.[1] He also cited empirical data that when patients with schizophrenia developed seizures, their psychosis was relieved. A Hungarian colleague Julius Nyirö followed these observations by injecting blood from patients with schizophrenia into those with epilepsy to stop their fits; this experiment failed.[1] Thinking that the antagonism would work in the opposite direction, Meduna explored ways to induce seizures, first using intramuscular injections of camphor dissolved in oil at Budapest's Royal National Hungarian Institute of Psychiatry and Neurology (Lipotmezö) in January 1934.

Forty-five minutes after an intramuscular injection, the subject exhibited a grand mal seizure. Meduna's first patients had been catatonic for many years, and after several treatments, they became lucid and left the hospital. By 1935, Meduna reported an experience with 26 patients—10 had recovered and 3 showed great improvement.[2] He believed that the seizures, not the camphor, were the therapeutic agent. When he became aware that water-soluble pentylenetetrazol (Metrazol, cardiazol) rapidly and more reliably produced seizures on intravenous injection, he abandoned camphor.[3]

Meduna's report aroused international interest, and many physicians made the pilgrimage to Budapest. After Lucio Bini's visit, he returned to Rome, and with Ugo Cerletti, they induced seizures using electricity. The first human inductions beginning on May 15, 1938 showed more assured seizures with simple devices—a clock to time and a rheostat to either enhance or decrease the intensity of household currents.[4] By the early 1960s, electroconvulsive therapy (ECT) had replaced Metrazol inductions of seizures.

In 1957, an inhalant convulsive anesthetic flurothyl (Indoklon) emerged. It was a fluorine-substituted diethyl ether that induced the loss of consciousness after a few breaths. Continued inhalation elicited a grand mal seizure.[5,6]

Flurothyl inhalation, Metrazol injection, and electric stimulation reliably produced seizures with indistinguishable clinical, electroencephalogram (EEG), and neuropsychological effects. In one study, the EEG changes during seizures induced by Metrazol, flurothyl, and ECT were reported as "strikingly similar," and it was proposed that "these agents act on the human brain through a common operating mechanism."[7]

Metrazol injection and flurothyl inhalation were effective seizure induction agents but were discarded and are not in clinical use today. Electrical inductions were easier and less expensive. In today's clinical practice, pharmacotherapy-resistant mood disorder in psychiatric patients is a continuing treatment challenge, particularly if the patients will not accept ECT. This review was encouraged by renewed interest in ketamine and isoflurane anesthetics and neurostimulation methods as treatments for patients with medication-resistant mood disorders.

PENTYLENETETRAZOL (METRAZOL)

The rapid intravenous injection of 10% Metrazol solution produced a grand mal seizure within a few minutes.[8–15] Dosing and frequency of treatments varied. Some used dosages of the 10% solution calibrated as 1 mL per 30 kg body weight in the first injection (up to 5 mL), although it was acknowledged that there was no relationship between body weight and the dose that

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The Seizure, Not Electricity, Is Essential in Convulsive Therapy

The Flurothyl Experience

Max Fink, MD

Background: For more than 50 years, research in convulsive therapy has been focused on the impact of electricity and seizures on memory and not on brain chemistry or neurophysiology. Brief pulse and ultra-brief pulse currents replaced sinusoidal currents. Electrode placements were varied, energy dosing was altered, and electricity was replaced by magnetic currents.

Method: The published experiences and archival records of seizures induced by camphor, pentylenetetrazol, and flurothyl are reviewed and compared with the changes induced by electricity.

Findings: The clinical efficacy of chemically induced seizures is equal to that of electrical inductions. Seizure durations are longer, and impairment of cognition and memory is less. Electroconvulsive therapy replaced chemical treatments for ease of use, not for greater efficacy or safety.

Conclusions: The brain seizure, not the method of induction, is the essential element in the efficacy of convulsive therapy. Seizure induction with chemicals avoids the direct effects of electricity on brain functions with lesser effects on cognition.

Reexamination of chemical inductions of seizures as replacements for electricity is encouraged.

Key Words: convulsive therapy, ECT, flurothyl, pentylenetetrazol

(*J ECT* 2014;30: 91–93)

Ladislas Meduna, a Hungarian neuroscientist, induced epileptic seizures in psychiatric patients with severe illness in 1934. It was a dramatic but little recognized milestone in the history of medicine. Spontaneous epileptic seizures were long considered a malignant stroke from the gods, dangerous to an individual's health and welfare. To voluntarily induce a grand mal seizure in man had not been done before Meduna responded to his finding of a surfeit of brain glia concentrations in patients with epilepsy and an insufficiency in those with schizophrenia.[1] He envisioned repeated inductions of seizures as increasing brain glial concentrations, redressing the deficiency, and relieving the psychosis.

Meduna first used intramuscular injections of camphor, but such inductions were not assured, with many injections failing to develop a seizure. His second method, intravenous pentylenetetrazol (Metrazol), elicited more assured seizures, and it quickly became the principal induction method. As more clinicians followed his lead, seizure induction by pentylenetetrazol was widely used throughout the world.[2]

An electrical induction of seizures was described in 1938. These inductions were even more reliable, and by the mid-1940s, electroconvulsive therapy (ECT) had become the accepted seizure induction method. Patient fears, risks of bone fractures, and prolonged seizures were mitigated by premedication with barbiturate sedation and succinylcholine muscle inhibition.[3] By the 1950s, ECT was a principal treatment of patients with severe mental illness until overridden by the tsunami of new psychoactive drugs.

In 1957, an inhalant anesthetic hexafluorodiethyl ether (flurothyl, Indoklon) was reported to induce grand mal seizures. An extensive clinical experience quickly followed with 4 systematic comparisons of flurothyl inductions and ECT. Seizure durations were longer, immediate cognitive effects were less, and adverse effects were fewer for flurothyl than for ECT.[4–7] However, because electrical inductions were easier to apply and were less expensive, interest in flurothyl waned and modified ECT became the main seizure induction treatment of patients with psychiatric illness.[3]

The principal hazards of ECT were burns at electrode sites; fractures of the jaw, shoulder, and limbs; headache; prolonged seizures; and fear. Surprisingly, little attention was paid to the effects on memory.[8,9]

By the mid-1970s, however, public hostility to *shock therapy* and *electroshock* engendered by the film *One Flew Over the Cuckoo's Nest*, attacks by Scientologists, as well as the hostility of psychotherapists and psychologists promoting the "memory loss, memory loss" mantra so dominated public and professional concerns that academic attention shifted from the phenomenology of the seizure and its impact on behaviors to manipulations of the electric currents and electrode placements. Unilateral electrode placement over the non–dominant hemisphere to avoid the impact of electricity on the brain's memory and speech centers quickly confirmed that the electricity path did directly affect brain functions. Effects on cognition were attenuated but at the cost of lesser clinical efficacy and longer courses of treatments.[10–12]

By the 1980s, sinusoidal electric currents were replaced by brief-pulse square wave currents. These are the principal form of electricity delivered by modern devices.

The search for dosing with minimal electrical energies was tested by calibrating an individual's seizure threshold (ST).[13] The ST was determined by first applying energies below the anticipated threshold using the knowledge that ST was low in childhood and gradually rose with age. Patients were anesthetized, and the first induction attempted at a level that would not induce a seizure. Energies were increased by graduated amounts under the same anesthesia until a seizure was elicited. That energy level that just induced a seizure was defined as the *seizure threshold*. Subsequent dosing was set at multiples of this calibrated ST.

Energies set at 1.5× and 2.5× ST with right unilateral (RUL) electrode placements elicited short seizure durations, poor quality of electroencephalographic (EEG) criteria, and minimally effective clinical outcomes.[13] To achieve an efficacy for RUL treatments equivalent to that of bilateral electrode placement required dosing at 8 to 12× ST. At these doses, the anticipated benefit on cognitive tests was lost.[14]

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These are the first two. In 2014, Fink and Kathryn Cooper, then a medical student who was to graduate in 2016, published these reviews on flurothyl convulsive therapy.

Psychiatric Times

Revive Flurothyl Inhalation Therapy

March 19, 2014

Max Fink, MD, Edward Shorter, PhD

Psychiatric Times, Vol 31 No 3, Volume 31, Issue 3

Acknowledgement-We are indebted to Kathryn Cooper, BS, Class of 2016 of the University of Rochester School of Medicine in New York for a detailed review of the clinical experience with chemical inductions of seizures in man.

A reexamination of flurothyl infusions holds promise for improved resolution of severe mood disorders, as well as for a greater understanding of the mechanism of their pathophysiology.

Together with the psychiatry historian Edward Shorter Fink also tried to introduce a less scary name, Flurothyl Inhalation Therapy.

From the Department of Psychiatry (Head: Professor Jan-Otto Ottosson), University of Umeå, Umeå, Sweden

Björn Laurell & Carlo Perris (together with Jan-Otto Ottosson and Giacomo d'Elia)

COMPARISON OF ELECTRIC AND FLUROTHYL CONVULSIVE THERAPY I-V

I. Seizure and post-seizure electroencephalographic pattern
II. Antidepressive effect
III. Anterograde amnesia
IV. Retrograde amnesia
V. Confusion and other side-effects

Acta Psychiatrica Scandinavica 1970;213:1-79

From the Department of Psychiatry (Head: Professor Jan-Otto Ottosson), University of Umeå, Umeå, Sweden.

COMPARISON OF ELECTRIC AND FLUROTHYL CONVULSIVE THERAPY

I. Seizure and post-seizure electroencephalographic pattern

By Björn Laurell and Carlo Perris

The seizure activity in electroconvulsive therapy (ECT) is followed by characteristic electroencephalographic (EEG) changes. After the seizur an initial phase of electrical silence can be delimited from a phase o delta waves, which first appear in bursts and then become continuous The delta waves are succeeded by faster activity with a gradual shift t the pre-seizure pattern (see *Kirstein & Ottosson* 1960 for references) Analogous patterns have been described after flurothyl (Indoklon) induce seizures (ICT), but there are only few comparative studies (*Esquibel et al* 1958, *Krantz et al.* 1958, *Chatrian & Petersen* 1960, *Scanlon & Matha* 1967).

Two early studies (*Esquibel et al.* 1958, *Krantz et al.* 1958), probabl describing the same patients, report the impression of a diminished amoun of delta wave activity in the post-seizure pattern in ICT compared wit ECT. However, the assessment was not standardized and the sample were small. *Chatrian & Petersen* (1960), studying 5 schizophrenic patient with implanted intra-cerebral electrodes, reported identical electrographi patterns for flurothyl, pentylenetetrazol (Metrazol) and electrical technique both during and at various intervals after the seizure. One conclusion wa that the total duration of the seizure appeared to be determined b individual factors rather than by the nature of the convulsant. However this conclusion was based only upon two intraindividual comparison between ECT and ICT. *Scanlon & Mathas* (1967) in an interindividua comparison between ECT and ICT in 4 patients studied the EEG-patter during and one hour after the treatments, each patient receiving 1 treatments. They found that the flurothyl-induced seizures lasted longe and that the EEG-pattern during seizure contrasted in form compare with the electrically induced ones, but the post-ictal changes were similar No details are given. The longer duration of flurothyl-induced seizure is in agreement with clinical observations (*Karliner & Padula* 1962 *Lapolla et al.* 1965, *Gander et al.* 1967, *Rose & Watson* 1967, *Small et a*

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COMPARISON OF ELECTRIC AND FLUROTHYL CONVULSIVE THERAPY

II. Antidepressive effect

By Björn Laurell

Conflicting views are expressed about whether or not there are appreciable differences between clinical results obtained with flurothyl (ICT) and electroconvulsive treatment (ECT). It has been maintained that ICT is superior to ECT in treating chronic depressive, schizoaffective and paranoid states (*Karliner & Padula* 1960, 1963, *Rosenberg* 1962, *Bell* 1965, *Dolenz* 1965, *Freund & Warren* 1965, *Azuela et al.* 1967, *Karliner* 1963, 1966). However, all these studies are non-controlled. In controlled studies the therapeutic effect of ECT and ICT is found to be about the same (*Kurland et al.* 1959, *Fink et al.* 1961, *Spreche* 1963, *Gander et al.* 1967, *Small et al.* 1968).

Kurland et al. (1959) made a comparison among 180 unselected patients divided into two groups, 90 in each, one treated with ECT, the other with ICT. The mean number of treatments, approximately 10.5, was equal in the two groups and the clinical effectiveness compared on a global psychiatric rating scale after the treatment series and 3 months later was fairly equal. However, the results are not related to the different diagnostic groups and the design was not double-blind. The study by *Fink et al.* (1961) comprising 27 patients, 12 treated with ECT and 15 with ICT, also concerns unselected patients and the evaluation of the clinical results is not related to different diagnostic categories. The study by *Spreche* (1963) concerns psychotic depressions. Two groups, 12 patients in each, received series either of ECT or ICT, and measurements of effects on depression were accomplished by the use of two different inventories. The mean number of treatments and the therapeutic effect was similar in the two groups. In the study by *Gander et al.* (1967), comprising 15 depressive and 1 schizophrenic patient, an intraindividual comparison was made. The patients received alternatingly ECT and ICT and a clinical assessment of degree of improvement was made after each treatment and found to be similar after ECT and ICT. It may be questioned whether this design is adequate for an evaluation of the clinical

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COMPARISON OF ELECTRIC AND FLUROTHYL CONVULSIVE THERAPY

III. Anterograde amnesia

By Björn Laurell

Memory disturbances after convulsive treatments may be classified into three categories (see *Cronholm* 1969): (i) memory disturbance due to the unconsciousness during the treatment and the profound confusion immediately after; (ii) retrograde amnesia, i.e. reduced ability to remember what happened before the treatment; (iii) anterograde amnesia, i.e. a reduced ability to remember what is learned after the treatment.

In anterograde amnesia the principal memory disturbance concerns retention as shown in a series of investigations by *Cronholm* and colleagues (*Cronholm & Molander* 1957, *Cronholm & Blomquist* 1959, *Ottosson* 1960, *Cronholm & Molander* 1964). In endogenous depression there is an impairment of learning but normal retention. After ECT a double effect is obtained: learning is improved, parallel to amelioration of the depressive state, and retention impaired (*Cronholm & Ottosson* 1961). As shown by *Ottosson* (1960) the impaired retention is partly a direct, i.e. not seizure-related, effect of the electric stimulation and dependent on its strength. Since the memory impairment is to be regarded as a side-effect in the treatment of endogenous depression (*Ottosson* 1968) a treatment technique where the electric stimulus is eliminated may cause less memory impairment, a fact indicated already by unsystematic observations during metrazol therapy (see e.g. *Silfverskiöld & Dencker* 1957). Comparative investigations of ECT and ICT have also included memory functions but none, so far, retention.

In comparative studies by *Kurland et al.* (1959), *Fink et al.* (1961) and *Scanlon & Mathas* (1967) after series of ECT and ICT in unselected patients the memory impairment, measured by the Wechsler-Bellevue Memory Scale and the Graham-Kendall Memory-for-Designs Test, was similar in both groups. *Spreche* (1963), also using the Wechsler Memory Scale, found somewhat greater memory impairment in the ICT-group after 5 treatments, but after the complete series only a minor difference. In a psychomotor test, assumed to measure degree of "organic brain

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COMPARISON OF ELECTRIC AND FLUROTHYL CONVULSIVE THERAPY

IV. Retrograde amnesia

By Björn Laurell

Retrograde amnesia in convulsive therapy refers to impaired remembering of what is learned before the treatment. It has been assumed that learning is followed by a period of fixation or consolidation which is especially sensitive to disturbing influences (see *Cronholm & Lagergren* 1959, *Cronholm* 1969) and, accordingly, recent memories suffer the greatest loss Whereas a great number of investigations on retrograde amnesia in electri convulsive therapy (ECT) have been published (see surveys in *Cronholm & Lagergren* 1959, *Williams* 1966), all clinical studies on memory disturbance after flurothyl (Indoklon) convulsive therapy (ICT) deal with anterograde amnesia (see *Laurell* 1970). Only in an investigation on mice has retrograde amnesia after flurothyl-induced seizures been studied and was found to be more pronounced than after electrically induced seizures (*Bohdanecky et al.* 1968).

In a series of investigations *Cronholm* and colleagues, using a memory test battery constructed by *Cronholm & Molander* (1957), have studied retrograde amnesia after different modifications of ECT (*Cronholm & Molander* 1961, *Cronholm & Ottosson* 1961, 1963 *a*). When using an overdose of electrical stimulus as in "counter-shock"-treatment the retrograde amnesia increased (*Cronholm & Ottosson* 1961), but when the electrical stimulus was reduced as in "ultrabrief stimulus technique" the retrograde amnesia decreased (*Cronholm & Ottosson* 1963 *a*). The conclusion was that the retrograde amnesia was to a certain extent related to the amount of electrical energy used in the treatment. On the basis of these findings it was suggested (*Ottosson* 1967, 1968) that convulsive treatments, elicited without using an electrical stimulus but in the original chemical way, should cause less memory impairment than ECT.

The purpose of the present investigation was to compare retrograde amnesia after ECT and ICT.

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COMPARISON OF ELECTRIC AND FLUROTHYL CONVULSIVE THERAPY

V. Confusion and other side-effects

By Björn Laurell

Since flurothyl (Indoklon) was introduced as a convulsive agent (*Krantz et al.* 1957 *a, b*) several comparative studies have been published of flurothyl convulsive therapy (ICT) and electroconvulsive therapy (ECT). One of the pertinent questions is whether the two treatments differ with regard to side-effects, especially confusion.

The first studies gave the impression that ICT produced less confusion than ECT (*Esquibel et al.* 1958, *Kalinowsky et al.* 1958, *Krantz et al.* 1958, *Dolenz & Sprehe* 1963, *Azuela et al.* 1967). On the other hand, *Karliner & Padula* (1962) observed more confusion after ICT than after the same number of ECT-treatments. *Dolenz* (1967) reported some cases with delayed confusion after ICT. *Gander et al.* (1967) in a pilot study among 16 patients made an intraindividual comparison between ECT and ICT, the patients receiving 44 treatments with ECT and 52 with ICT. Confusion occurred after 6 out of 32 treatments with a high dose (1.5—3 ml) of flurothyl, 2 out of 20 with a low dose (0.5 ml) and not at all after ECT-treatment. Memory disturbance, referred to as late side-effects, occurred after 6 treatments using a high dose of flurothyl, after 3 using a low dose and after 5 ECT-treatments. However, since the number and order of the treatments in the 16 patients are not mentioned, and the measurement of confusion and memory disturbance is not described, no definite conclusions can be drawn. In a double-blind comparative study *Small et al.* (1968) found a much lower incidence of confusion and memory loss associated with ICT than with ECT as established by clinical observation, patients' reports and psychological tests. There were 50 patients treated with series of ICT (range 9—37) and another 50 patients with series of ECT (range 7—38). 10 per cent of the ICT-treatments (all grand mal seizures) caused confusion according to estimation by nurses 6 hours after the last treatment, compared with 29 per cent of the ECT-treatments. As in the study by *Gander et al.*, confusion is not defined and the number of patients with confusion is not given.

The third attachment is the study by Björn Laurell in Umeå, lead by Jan-Otto Ottosson. This was part of a large study of flurothyl convulsive therapy by Laurell, and right unilateral ECT by d'Elia, both compared to bitemporal ECT.

Flurothyl Induced Seizures: A Viable Alternative to ECT

Max Fink, M.D.

Conflicts of Interest: None

March 10, 2022

Max Fink 2022-1

May 4, 2022

Flurothyl Inhalation Therapy

Resurrecting An Alternative to Electricity Induced Seizures

Amidst the exciting introductions of psychoactive drugs that marked the psychopharmacologic revolution of the 1950s and 1960s, was a passing interest in a homolog of diethyl ether, the inhalational anesthetic introduced to American surgery in the 1840s. In 1953 the Baltimore pharmacologist John Krantz synthesized flurothyl, hexafluorodiethyl ether $(C_2H_5)_2O$. Expecting a variation of anesthesia, the animal losing consciousness rapidly, he was surprised by a grand mal seizure that immediately followed after a few additional breaths. Recovery was quick and the first trials offered no prolonged effects.

Inducing grand mal seizures to relieve psychosis in the psychiatric ill had been demonstrated in 1934 using intramuscular camphor and intravenous pentelenetetrazol (Metrazole) by Ladislas Meduna. His report to an international audience at Muensingen in 1936 and the publication in 1937 of a 50% recovery rate in 110 hospitalized psychiatric ill encouraged worldwide enthusiasm to induce seizures for the severe mentally ill. Italian psychiatrists Ugo Cerletti and Lucio Bini developed the electrical induction of seizures in May 1937 that developed to today's electroconvulsive therapy (ECT) in worldwide use.

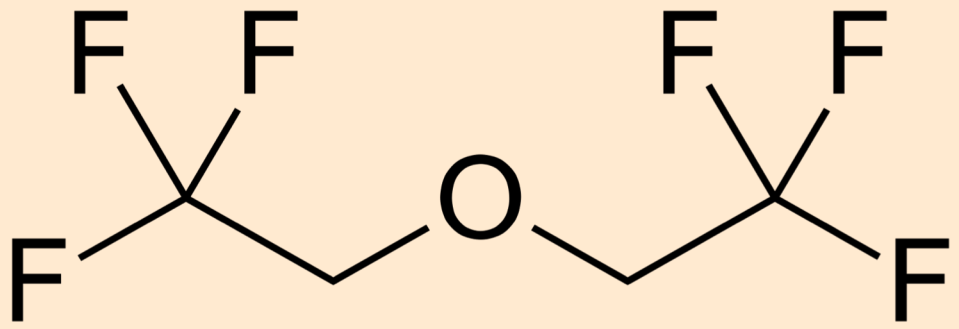
Krantz approached Albert Kurland, the psychiatrist treating severe mentally ill at Spring Grove State Hospital in Catonsville, Maryland to undertake human trials. Inducing seizures delivering flurothyl through a facemask elicited grand mal seizures equivalent in length, in cardiovascular effects, time to recovery, and changes in the EEG with patients treated with ECT. Three other RCT studies compared flurothyl-induced seizures with ECT, confirming the Krantz/Kurland findings.

Remission Rate	50%-55%	47%-62%
Seizure Duration	24-55 sec	60-90 sec
Memory-anterograde	No difference	
Memory-retrograde	Greater effect	Lesser effect

Fink wrote to me that he «had planned to present a discussion of flurothyl at ISEN, but reconsidered and did not present the story.” But he did write an essay, to the right here, and collected a few slides, which he sent to me. This is his title-slide.

Flurothyl (Indoklon)

Hexafluoro-diethyl ether



Max Fink 2022-2

Slide 2 shows the simple formula of flurothyl.

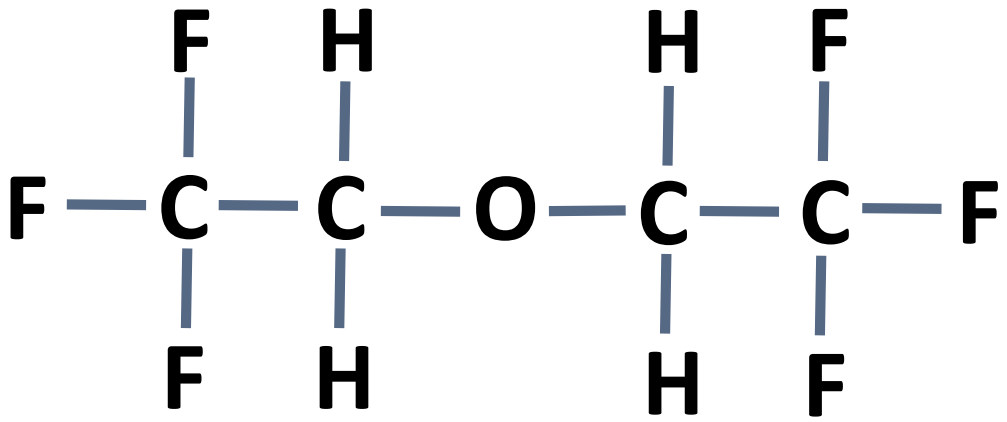
ethyl alcohol $\mathbf{CH_3CH_2OH + CH_3CH_2OH}$

$- H_2O \Downarrow$

diethyl ether $\mathbf{CH_3CH_2OCH_2CH_3}$

$- 6H \Downarrow + 6F$

hexafluorodiethyl ether = flurothyl (Indoklon) $\mathbf{CF_3CH_2OCH_2CF_3}$



You take two ethyl alcohol molecules and six fluor atoms, and vips, you have flurotyl, or Indoklon. In his essay Fink writes: «The effects of flurothyl were rapid. After a few breaths the subject was asleep, and 2 to 3 more and the seizure was induced. The sequence occurred in less than a minute."

History of Flurothyl Treatment

1953 LSD tested

1954 Chlorpromazine in clinics

1957 Imipramine in clinics

1956 Flurothyl created by John Krantz

1957 First clinical trials in Baltimore by Albert Kurland

1959 RCT Albert Kurland

1959 Office trials Lothar Kalinowsky, William Karliner

1961 RCT Hillside Hospital Max Fink

1968 RCT Joyce Small

1970 Memory study - Jan-Otto Ottosson and Björn Laurell

Max Fink 2022-3

Flurothyl was created by John Kranz, and Louise Speers according to Dolenz, in Baltimore in the early 1950s. The first clinical trial was done by Albert Kurland in Baltimore. Then followed office trials by Kalinowsky and Karliner, three RCTs in Baltimore and New York, and a systematic study by Laurell and Ottosson in Umeå.

Flurothyl – first clinical reports 1957

«four patients who were suffering with mental disturbances in which electroshock therapy was indicated were subjected to inhalation of hexafluorodiethyl ether.»

Krantz, Truitt, Speers, Ling. New pharmacoconvulsive agent. Science Aug 23 1957;126:353-4

Esquibel, Krantz Jr, Truitt, Kurland. The use of hexafluorodiethyl ether (Indoklon) as an inhalant convulsant. Am J Psychiatry Nov 1957;114:461

«HISTORY ... In the early 50's, Dr. Louise Speers[4] first synthesized Indoklon while working with fluorinated ethers in the hope of finding the ideal anesthetic agent. ... Pharmacologist John Krantz[4,12] and his co-workers demonstrated that Indoklon could produce convulsions regularly and dependably without tolerance in animals, and without harmful effects. ... its usefulness as a convulsant agent in the treatment of the mentally ill was first demonstrated hy Dr. Albert Kurland at Spring Grove State Hospital in 1956.»

Dolenz BJ. Indoklon – a clinical review. Psychosomatics 1965;6:200-5:

I think these are the first clinical reports from 1957, in Science and the American Journal of Psychiatry, and a short history from a 1965 review.

ECT and Flurothyl Seizures

	ECT	*Flurothyl*
Remission Rate	**50%-55%**	**47%-62%**
Seizure Duration	**24-55 sec**	**60-90 sec**
Memory - Anterograde	**No difference**	
Memory - Retrograde	**Greater effect**	**Lesser effect**

Max Fink 2022-4

The points are that flurothyl seizures are equally effective as bitemporal ECT with lesser effect on retrograd memory. Seizure duration was longer.

Among many clinical trials exploring the effects of flurothyl, the 4 systematic studies compared 173 subjects receiving ECT and 170 flurothyl. The remission rates for both seizure induction methods were approximately 50% and considered clinically equivalent. The flurothyl inductions had measurably less impairment of psychological tests and fewer patient complaints.

Kathryn Cooper and Max Fink

The chemical induction of seizures in psychiatric therapy:
Were flurothyl (Indoklon) and pentylenetetrazol (Metrazol) abandoned prematurely?
J Clin Psychopharmacol 2014;34:602-7

1	*Kurland et al* *Baltimore, USA*	*A comparative study of hexafluorodiethyl ether (Indoklon) and electroconvulsive therapy* *J Nerv Ment Dis 1959;129:95-8*
2	*Fink et al* *New York, USA*	*Inhalant-induced convulsions: significance for the theory of the convulsive therapy process* *Arch Gen Psychiatry 1961;4:259-66*
3	*Small et al* *Indianapolis, USA*	*A double-blind comparative evaluation of flurothyl and ECT* *Arch Gen Psychiatry 1968;19:79-86*
4	*Laurell (&Ottosson)* *Umeå, Sweden*	*Flurothyl convulsive therapy* *Acta Psychiatr Scand Suppl 1970;213:1-79*

This is a summary of the four systematic studies: «Among many clinical trials exploring the effects of flurothyl, the 4 systematic studies compared 173 subjects receiving bitemporal ECT and 170 flurothyl. The remission rates for both seizure induction methods were approximately 50% and considered clinically equivalent. The flurothyl inductions had measurably less impairment of psychological tests and fewer patient complaints».

TABLE IV. RESULTS OF INDOKLON TREATMENT IN PSYCHOTIC PATIENTS

Dolenz BJ. Indoklon – A Clinical Review. Psychosomatics 1965;6:200-5

Author	Rx. & No.	Diagnosis	No. of Patients	Results		
				Excellent	**Good**	No Change or Poor
Krantz et al 1958	Inhalation	Chronic Schizophrenia	13	2	11	
	(12)	Psychotic Depression	5	3	2	
	(15)	Catatonic Schizophrenia	4	4		
	(25)	Involutional Depression	3		2	1
Karliner 1963	Intravenous	Schizo. Affective	14	7	6	1
	(13)	Schizophrenic	50	13	34	3
	(80)	Manic Depressive	16	10	5	1
	Inhalation	Schizo. Affective	4	3	1	
	(13)	Schizophrenic	59	15	43	1
	(79)	Manic Depressive	16	11	4	1
Kurland 1960	Intravenous	Chronic schizophrenia	3		2	1
	(8)	Psychotid Depression	6	2	3	1
		Involutional Depression	3	2	1	
	(17)	Catatonic Schizophrenia	5	1	3	1
Padula 1963	Inhalation	Schizophrenic	89	16	70	3
	(101)	Manic Depressive	3	3		
Dolenz		Involutional Depression	1			
*	(14)	Psychotic Depression	33	22	10	1
	(51)	Paranoid Schizophrenic	4	3	1	1
		Chronic Schizophrenic	7	2	5	
		Total	338	**119**	**203**	16

Recovery or Excellent - Premorbid personality in all respects of interpersonal relationships.
Good - Premorbid personality, but not in all areas of previous functioning level.
*31 had prior somatic treatment and were treatment problems.

Results in psychotic patients were excellent in 35% and good in 60%. Both inhalation and intravenous Indoklon were used.

Advertising 1960s

Psychiatric News

Official Newspaper of the AMERICAN PSYCHIATRIC ASSOCIATION

Pilot Issue — Washington, D. C. — September 1965

INDOKLON (FLUROTHYL)

(bis (2, 2, 2-trifluoroethyl) ether)

a more effective form of treatment for some

"It is felt that the greater effectiveness of Indoklon may be due to its effect on the entire brain, whereas electroshock therapy probably affects only the cerebral cortex." (1)

a preferred treatment to electroshock for many

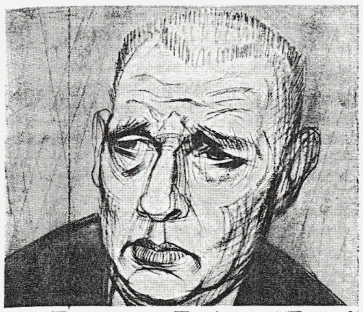
"In all cases, ready acceptance of the treatments was a characteristic feature. This was marked in those patients who feared and resisted electrotherapy." (2)

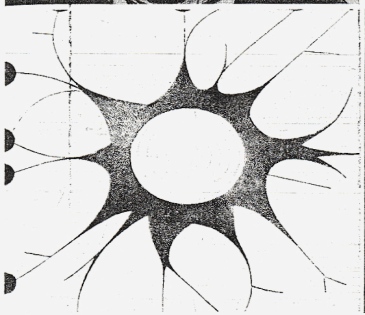
INDOKLON pharmacoconvulsive therapy has been used since 1956. An alternate to electroshock in the treatment of mental illness, administration of Indoklon is by inhalation. Seizures modified by anesthetics and muscle relaxants are soft and free of fractures. Indoklon is dependable in producing grand mal seizures. Late convulsion, common to some pharmacoconvulsive agents, is not present. Write for Brochure No. 8180 and complete article reprints No's. 390 and 391—see references (1) and (2) — Ohio Chemical (a division of Air Reduction Company, Inc.) Madison, Wis. 53701.

Contraindications for Indoklon are similar to those for electroshock therapy. Indoklon should not be given to a patient with even a very mild upper respiratory infection. Indoklon should not be given to any patient with severe cardiovascular, hepatic, or renal disease. Indoklon should not be given to any patient with severe intraocular or intraspinal increase in pressure. Patients with abnormal body temperatures should be temporarily excluded from Indoklon therapy until the temperature returns to normal. Indoklon is not to be used with pregnant females. For information on use and dosage, refer to detailed instructions contained in product package. **Compatibilities** — no known incompatibilities with Indoklon have been reported.

References: (1) Kartiner, Wm.: Observations on the Use of Indoklon (accepted for publication April, 1964, by JOURNAL OF NEUROPSYCHIATRY). (2) Freund, J. C.; Warren F. J.: A Clinical Impression of Hexafluorodiethyl Ether (Indoklon) Following more than 800 treatments, DISEASES OF THE NERVOUS SYSTEM, Vol. 25, pp. 50-57, (January, 1965).

OHIO Ohio Chemical





whenever depression complicates the picture

Tofranil®

brand of imipramine HCl

hastens recovery

Geigy

In many seemingly mild physical disorders an element of depression plays an insidious etiologic or complicating role.

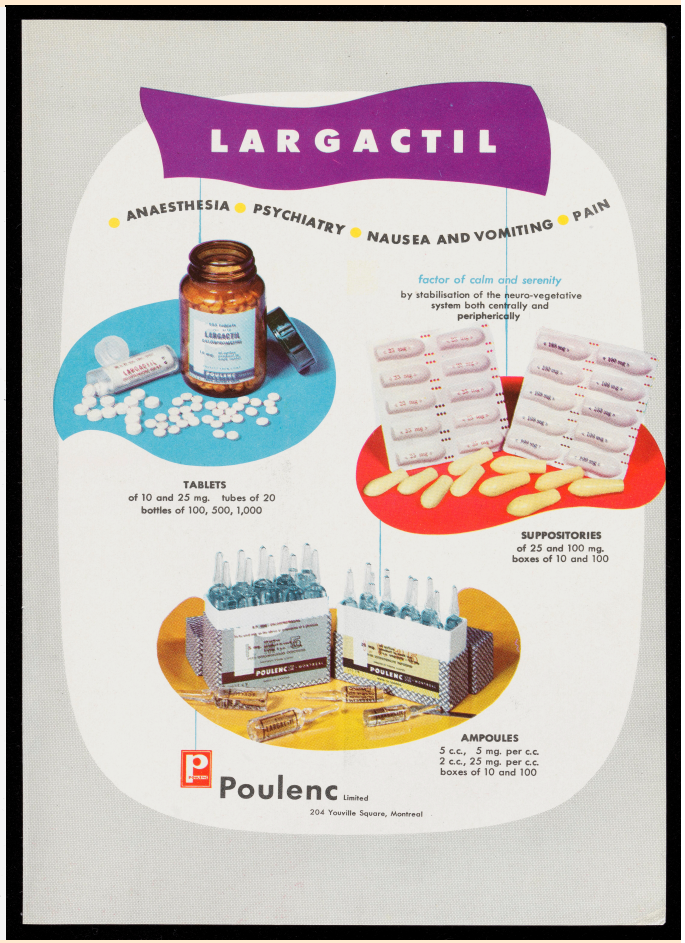
Because of its efficacy as an antidepressant, coupled with its simplicity of usage, Tofranil is admirably adapted to use in the home or office in these milder "depression-complicated" cases.

It is always wise to recognize that depression may be an underlying factor...that Tofranil may speed recovery in "hypochondriasis"; in convalescence when recovery is inexplicably prolonged; in chronic illness with dejection; in the menopausal patient whose emotional disturbances resist hormone therapy; and in many other comparable situations in which latent depression may play a part.

Detailed Literature Available on Request.

Tofranil®, brand of imipramine hydrochloride, tablets of 25 mg. Ampuls for intramuscular administration, 25 mg. in 2 cc. of solution.

Geigy, Ardsley, New York



Max Fink 2022-5

Flurothyl was produced by the Ohio Chemical Company under the name Indoklon, created from the words induction and klonic.

INDOKLON (FLUROTHYL)

Advertisement in Psychiatric News, Sep 1965 (Official Newspaper of the American Psychiatric Association)

a more effective form of treatment for some

«It is felt that the greater effectiveness of Indoklon may be due to its effect on the entire brain, whereas electroshock therapy affects only the cerebral cortex.» (1)

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Ohio Chemical

Those interested can read here the hole advertisement in Psychiatric News of the American Psychiatric Association.

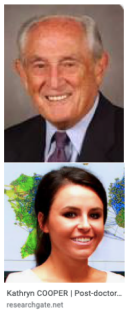
It seems to be a consensus ... that there is a tremendous margin of safety. No toxic conditions have been reported to date, and there have been no fatalities.
Patient acceptance of Indoklon in our experience has been excellent and the procedures ... safe and simple. Kalinowski[9] says, «In our experience, we were impressed by the fact that patients feel much more comfortable after this treatment than after ECT ... It seems that the unpleasant memory impairment is at least reduced by avoiding the electric current, and that the increasing fear of the treatment ascribed to the awakening from ECT is also diminished. If these observations are confirmed by further experience, Indoklon either by inhalation or by intravenous injection might easily replace ECT.»

Bernard J. Dolenz
Indoklon – A Clinical Review. Psychosomatics 1965;6:200-5

[9]Kalinowski and Hoch
Somatic Treatments in Psychiatry, New York, Grune and Stratton, 1961.

Dolenz, in 1965, wrote in his review on Indoklon that
«It seems to be a consensus ... that there is a tremendous margin of safety. No toxic conditions have been reported to date, and there have been no fatalities. Patient acceptance in our experience has been excellent and the procedures ... safe and simple.» Dolenz also refers to Kalinowski's impression that «patients feel much more comfortable than after ECT ... It seems that the unpleasant memory impairment is at least reduced by avoiding the electric current, and that the increasing fear of the treatment ascribed to the awakening from ECT is also diminished. If these observations are confirmed by further experience, Indoklon, either by inhalation or by intravenous injection, might easily replace ECT.»

It is unclear why intravenous flurothyl did not come into wider use. Less specialized equipment was required, and the smaller amounts of flurothyl could be precisely measured. Secondary convulsions were less likely, although this was not systematically studied.[47,48]



Kathryn Cooper and Max Fink

The chemical induction of seizures in psychiatric therapy: Were flurothyl (Indoklon) and pentylenetetrazol (Metrazol) abandoned prematurely? J Clin Psychopharmacol 2014;34:602-7

However, intravenous flurothyl, of unknown reasons, did not come into wider use, although less specialized equipment was required, the smaller amounts of flurothyl could be precisely measured, and secondary convulsions probably were less likely.

After inhalation, flurothyl was not metabolized and was discharged unchanged into the atmosphere, giving the treatment room an ethereal aroma. For observers who had seen the rapidity with which a few breaths induced sleep and then a seizure, the fear of inhalation inhibited its use. (Were flurothyl seizures be examined today, modern controlled air exchange in anesthesia suites would minimize this objection.)

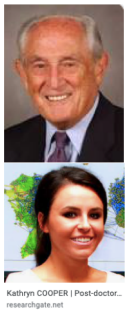
Max Fink

The seizure, not electricity, is essential in convulsive therapy: the flurothyl experience

J ECT 2014;30:91-3

After inhalation (and after injection I suppose), flurothyl was not metabolized and was discharged unchanged into the atmosphere, giving the treatment room an ethereal aroma. For observers who had seen the rapidity with which a few breaths induced sleep and then a seizure, the fear of inhalation inhibited its use.
Were flurothyl seizures be examined today, modern controlled air exchange in anesthesia suites would minimize this objection. No complications in the treatment personel were ever reported.

Cost played a role. Small and Small[50] cite personal communications with the Ohio Chemical Company in 1974 saying that the drug would no longer be supplied because of its high production costs and limited demand. Indeed, a chemical that needed to be produced in laboratories and distributed would be more expensive than a short burst of electricity from a wall socket.

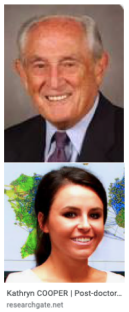


Kathryn Cooper and Max Fink
The chemical induction of seizures in psychiatric therapy: Were flurothyl (Indoklon) and pentylenetetrazol (Metrazol) abandoned prematurely? J Clin Psychopharmacol 2014;34:602-7

Cost also played a role. In 1974 the Ohio Chemical Company announced that Indoklon would no longer be supplied. Electricity was much cheaper and won the game.

Half a century ago,

the 2 inductions were considered equivalent in clinical efficacy, with flurothyl treatments associated with lesser effects on memory. Flurothyl inhalations were discarded because of a threatening aroma and higher cost and the ease of use of ECT.



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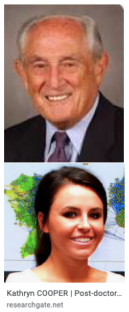
Half a century ago, the two inductions were considered equivalent in clinical efficacy, with flurothyl treatments associated with lesser effects on memory. Flurothyl inhalations were discarded because of 1) a threatening aroma, 2) higher cost, and 3) the ease of use of ECT.

During the past half century,

researchers, clinicians, and the public have been preoccupied with fears generated by electricity, of the association with death by electrocution and lightning, of the words “shock” and “electroshock,” and of the widespread concerns with losses of memories. Flurothyl offers effective relief of depression and psychosis without the risks associated with electricity. It encourages less threatening labeling, as in “inhalant treatments” or “intravenous chemotherapy.”



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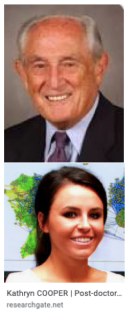
Conclusions: Persistent complaints of memory loss plague electricity induced seizures. Flurothyl induced seizures are clinically as effective without the memory effects associated with electricity. **Reexamination of seizure inductions using flurothyl in modern anesthesia facilities is encouraged** to relieve medication-resistant patients with mood disorders and catatonia.



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