NACT NORDIC ASSOCIATION FOR CONVULSIVE THERAPY

Achieving and maintaining remission
Tallin, May 25-27, 2022

Relapse after successful ECT

state of the art

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UPC KU LEUVEN

Overview

relapse
- *after successful ECT*
- *after M-ECT*

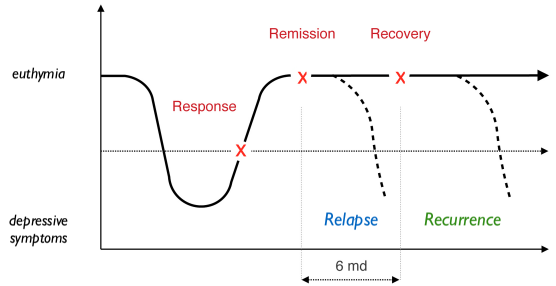
predicting relapse
- *biological markers*
- *patient characteristics*

preventing relapse

Conceptualization and Rationale for Consensus Definitions of Terms in Major Depressive Disorder

Remission, Recovery, Relapse, and Recurrence

Ellen Frank, PhD; Robert F. Prien, PhD; Robin B. Jarrett, PhD; Martin B. Keller, MD; David J. Kupfer, MD; Philip W. Lavori, PhD; A. John Rush, MD; Myrna M. Weissman, PhD



Relapse

return of symptoms of a still ongoing episode

occurs during the period of remission, but before recovery

Recurrence

appearance of an entirely new episode

can occur only during recovery

Relapse

following successful ECT - Meta-analysis

	3 months		6 months	
No R/	48%	2		
PLACEBO	63%	3	65%	7
			78%	4 modern RCT N=65

relapse rate % - number of studies - number of subjects

Jelovac et al (2013). Relapse following successful ECT for major depression: a meta-analysis. *Neuropsychopharmacology* 38, 12, 2467-74.

Relapse

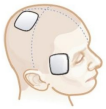
following successful ECT - Meta-analysis - Treatment reduces risk

	3 months	6 months	12 months	24 months
	27%	38% (17) 710	51% (8) 348	50% (3) 111
		37% (4) 146		

relapse rate % - number of studies - number of subjects

Jelovac et al (2013). Relapse following successful ECT for major depression: a meta-analysis. *Neuropsychopharmacology* 38, 12, 2467-74.

PHASE 1 RCT RUL UBP vs BP



ITT 116

BP N=58 — 26 Remitters

UBP N=58 — 24 Remitters

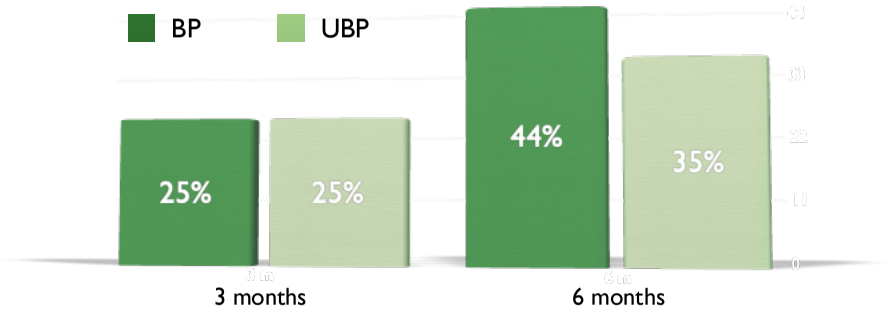
Spaans / Verwijk et al Efficacy and cognitive side effects after BP and UBP RUL ECT for major depression: a randomized, double-blind, controlled study. J Clin Psychiatry 2013; 74(11): e1029-36.

PHASE 2 Naturalistic Follow-up

3 M	N=24	N=20
6 M	N=23	N=20

Verwijk / Spaans et al. Relapse and long-term cognitive performance after brief pulse or ultrabrief pulse right unilateral ECT: A multicenter naturalistic follow up. J Affect Disord 2015; 184: 137-44.

RUL BP *vs* UBP *Relapse*



Verwijk / Spaans et al. Relapse and long-term cognitive performance after BP or UBP RUL ECT: A multicenter naturalistic follow up. J Affect Disord. 2015;184:137-44.

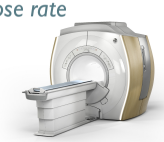
MODECT *6M-Relapse*

Mood Disorders in Elderly treated with ECT

- N=110, age ≥55 *mean 73*
- BP RUL 6ST 2x/w
- Remission 66.4% - N=73 *drop out N=11*
- Relapse study - N=67 *missing data N=6*

33%

6 mth relapse rate



Dols / Bouckaert et al. Early- and Late-Onset Depression in Late Life: A Prospective Study on Clinical and Structural Brain Characteristics and Response to ECT. Am J Geriatr Psychiatry 2017; 25(2): 178-89.

Wagenmakers et al. Psychotic LLD less likely to relapse after ECT. Journal of Affective Disorders 2020;276:984-990.

MODECT *5Y-Relapse*

Mood Disorders in Elderly treated with ECT

- N=110, mean age 73 - BP RUL 6ST 2x/w
- Response 78% - N=86
- 67% relapse
  - *median of 1 relapse*
  - *80% of relapse in first 2 years*

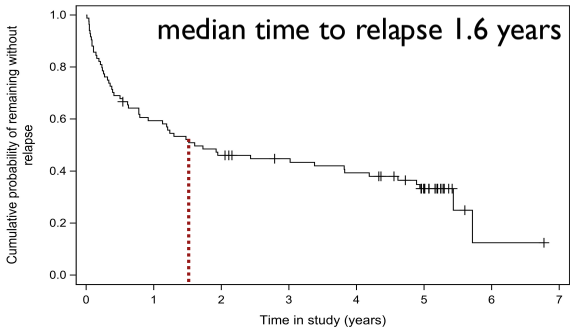
67%

5 year relapse rate

Lambrichts I Wagenmakers et al. Long-term outcome following electroconvulsive therapy for late-life depression: five-year follow-up data from the MODECT study Am J Geriatr Psychiatry (in press)

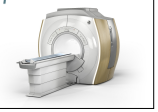
MODECT *5Y-Relapse*

Mood Disorders in Elderly treated with ECT



67%

5 year relapse rate

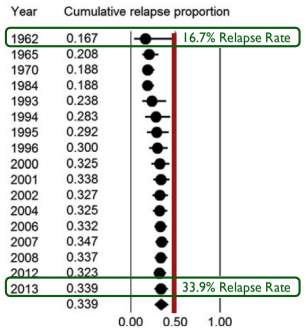


Lambrichts I Wagenmakers et al. Long-term outcome following electroconvulsive therapy for late-life depression: five-year follow-up data from the MODECT study. Am J Geriatr Psychiatry (in press)

Relapse

cumulative meta-analysis of relapse rates at 6 months following ECT across all eligible studies from 1962 onwards.

- Recent studies - higher relapse rates
  - changes in ECT populations *Sackeim, 1994*
    - *ECT once used as 1st-line treatment in often medication-naive patients*
    - *now reserved for difficult-to-treat depression, less likely to achieve full remission and prone to relapse*
      Fekadu et al, 2009



Jelovac et al (2013). Relapse following successful ECT for major depression: a meta-analysis. *Neuropsychopharmacology* 38, 12, 2467-74.

It is well established that ECT recipients have very high relapse rates …

Read & Arnold. Is Electroconvulsive Therapy for Depression More Effective Than Placebo? A Systematic Review of Studies Since 2009. *Ethical Human Psychology and Psychiatry* 2017;19:5-23.

Is *post-ECT* relapse higher

than post-meds relapse?

			12 month relapse rate (on M-Meds)	
Geddes et al 2003	meta-analysis AD-trials	*'clean'* RCT-population	16%	
STAR*D	remission after 1st step (SSRI)	*'real world'* recurrent, comorbidity non-resistant	34%	
	remission after >1 step	*'real world'* recurrent, comorbidity resistant	43-50%	
Jelovac et al 2013	meta-analysis ECT-trials	severely ill, resistant, suicidal…	50%	

Electroconvulsive therapy and psychiatric readmission in major depressive disorder – A population-based register study

Linnea Stenmark[1] | Charles H. Kellner[2] | Mikael Landén[3,4] | Irya Larsson[1] | Mussie Msghina[1,5] | Axel Nordenskjöld[1]

- 27.851 patients - 41916 admissions - ECT in 26.8%*of admissions*
- readmission @ 30 days and 90 days
  - *lower in ECT group* *(OR 0.90 and OR 0.93, respectively)*
  - decreased readmission risk a.o. *older age, psychotic features*
  - *below age 35* ECT associated with increased readmission risk

Relapse after stop M-ECT

3 retrospective studies

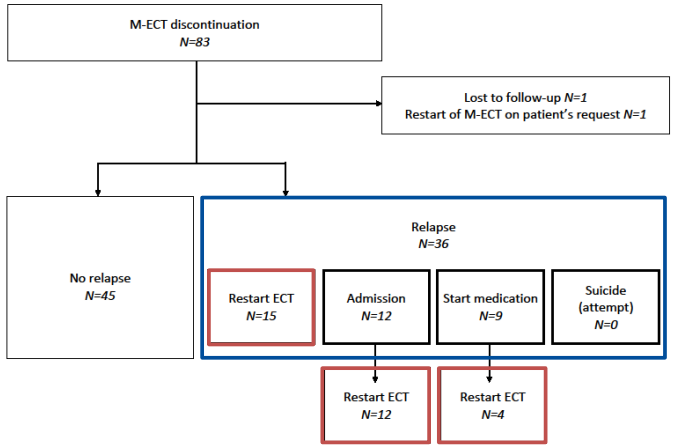
Author (year)	Sample size	Follow-up	Relapse definition	Relapse rate	Risk factor(s) for relapse
Huuhka et al (2012)	45	12 m	Rehospitalization Restart of ECT	44% *(all within 8 months)*	Diagnosis other than MDD
Martinez-Amoros et al (2020)	73	≥ 12 m	Rehospitalization Restart of ECT Suicide	49% *(18% within 6 months)*	Higher number previous episodes M-ECT interval <4 w
Cabelguen et al (2020)	16	≥ 6 m	Recurrence (new episode)	50% *(22% within 6 months)*	Not assessed

Relapse after *abrupt* stop M-ECT

3 prospective studies

Author (year)	Sample size	Follow-up	Relapse definition	Relapse rate	Risk factor(s) for relapse
Van de Velde et al (2021) *	33	3 m	Rehospitalization Restart of ECT	60%	Younger age M-ECT interval <2 w
Methfessel et al (2021) * # @	34	6 m	Rehospitalization	44%	Shorter time since index ECT
Lambrichts et al (2021) *	82	6 m	Rehospitalization Restart of ECT or meds Suicide (attempt)	43%	Psychotic disorder M-ECT interval <4 w

* abrupt discontinuation due to pandemic; # decision based on clinical condition; @ MDD, bipolar disorder, schizophrenia



43%

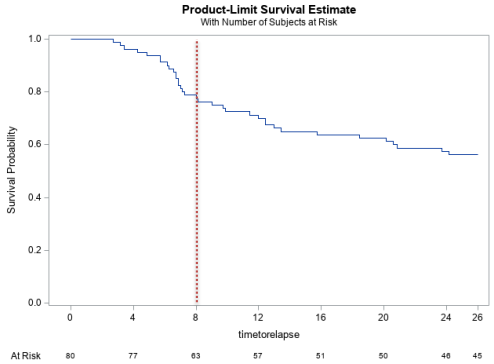
6-m relapse rate

89%

Restart of ECT
(15+12+4 / 36)

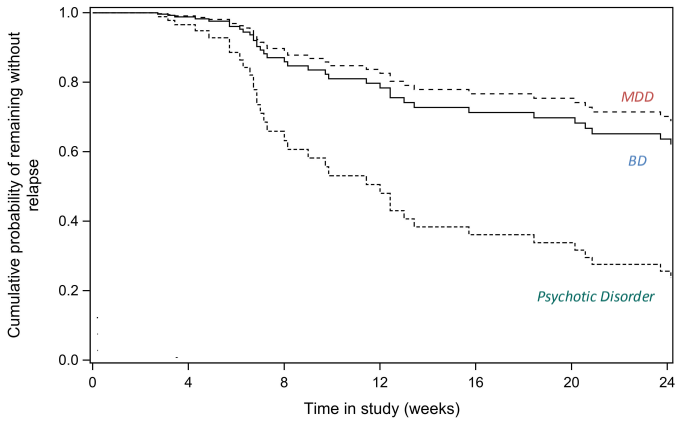
Time to relapse

Median=8.00 weeks (IQR=6,71)



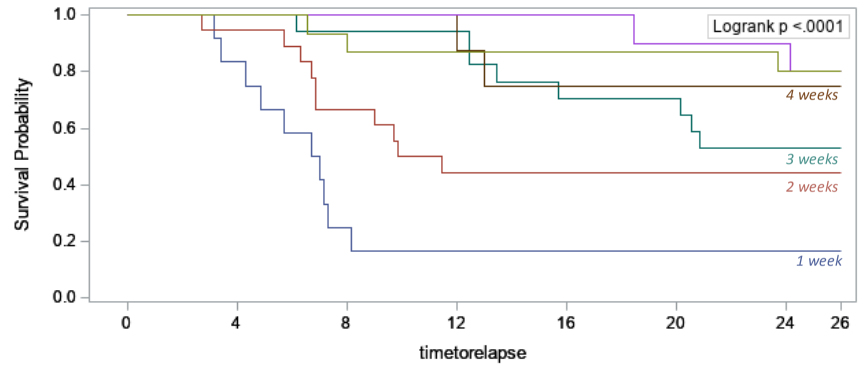
Mood disorders do better

Diagnosis - Cox proportional hazards model

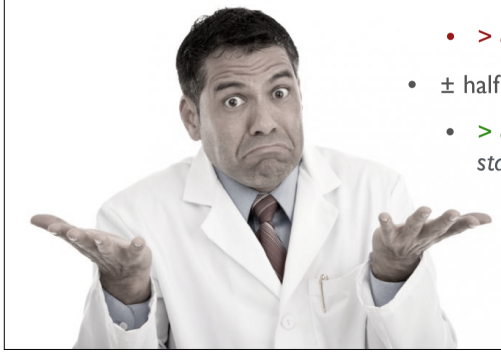


Shorter interval, earlier relapse

Kaplan-Meier survival curves by M-ECT-interval



What to conclude?



- ± half of the patients *relapsed*
  - *> consider continuation of M-ECT!*
- ± half of the patients did *not relapse*
  - *> consider stop M-ECT (especially in patients stable with a longer inter-treatment interval)*

Relapse

6 mth-relapse rate following successful ECT and MECT

38%

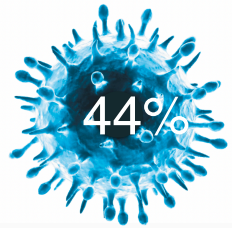
Jelovac et al (2013).
Relapse following successful ECT for major depression: a meta-analysis.
Neuropsychopharmacology 38, 12, 2467-74.

33%

MODECT
Wagenmakers et al. Psychotic LLD less likely to relapse after ECT.
Journal of Affective Disorders 2020;276:984-990.

28%

after M-ECT
retrospective studies



6 mth relapse rate
after abrupt COVID-related stop of M-ECT in 83 patients, mean age 69

Predictors

of relapse

- Longer duration of index episode *Martinez-Amoros et al 2012*
- Greater number of previous episodes *Martinez-Amoros et al 2012,Yang et al 2020, Jelovac et al 2021*
- Change RUL > BT during index course *Gruter & Grozinger 2018*
- Higher charge during index course *Gruter & Grozinger 2018*

Gruter & Grozinger M. [Determinants of relapse after electroconvulsive therapy in depressed patients]. Fortschr Neurol Psychiatr. 2018;86:711-717 / Martinez-Amoros et al. Long-term treatment strategies in major depression: a 2-year prospective naturalistic follow-up after successful electroconvulsive therapy. J ECT. 2012;28:92-97 / Yang et al. Risk Factors of Relapse After Successful Electroconvulsive Therapy for Taiwanese Patients With Major Depression. J ECT. 2020;36:106-110.

Predictors

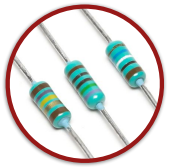
of relapse

- patient/illness characteristics
  - *age*
  - *medication-resistance*
  - *psychotic features*
  - *overgeneral memory*
  - *residual symptoms*
- biological markers
  - *REM sleep dysregulation*
  - *DST / TRH - test*
  - *heart rate variability*

Long-term prognosis

more favorable

age



resistance

psychotic features

Jelovac et al (2013). Relapse following successful ECT for major depression: a meta-analysis. *Neuropsychopharmacology* 38, 12, 2467-74.

N=61

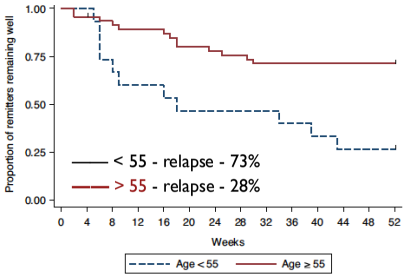
Remitters EFFECT-DEP BT vs RUL

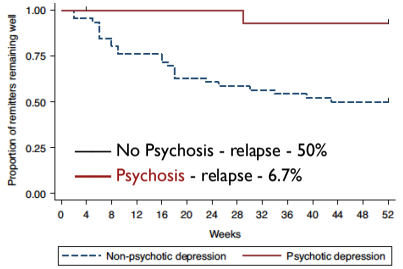
1 year naturalistic follow-up

39% relapse

Older age & psychotic features

predict a more favorable long-term outcome





Jelovac et al. Relapse following BT and high-dose RUL ECT for major depression. Acta Psychiatr Scand. 2021;144:218-229.

MODECT *6M-Relapse*

Mood Disorders in Elderly treated with ECT

- 73 remitters *66% of 110*
  - *Psychotic depression* *56%, N=41*
  - *Missing data on relapse* *N=6*
- Relapse study *N=67*
  - *6m-relapse 33%* *22/67*

Relapse rate psychotic depression 23.1% non-psychotic depression 46.1%

Wagenmakers et al. Psychotic LLD less likely to relapse after ECT. Journal of Affective Disorders 2020;276:984-990.

Readmission

- Readmission associated with a.o.
  - *younger age*
  - *being divorced / unemployed*
  - *comorbid anxiety disorder*
  - *non-psychotic depression*
  - *more severe symptoms before ECT*

N=7350

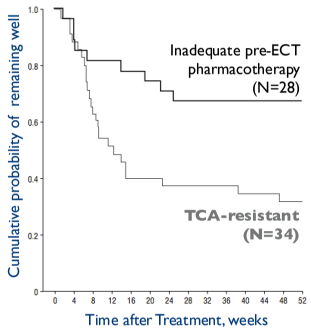
1.4 years

readmission N=4203 57.18 %

Brus et al. Lithium for suicide and readmission prevention after ECT for unipolar depression: population-based register study. BJPsych Open. 2019;5:e46.

Medication Resistance *Predicts* Relapse

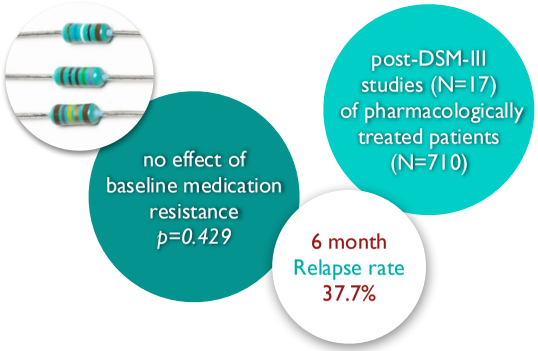
relapse 2x rate of patients who did not receive adequate TCA trial pre-ECT



- 12 month - relapse
  - *resistant patients 68.6%*
  - *patients who did not have adequate med trial before ECT 33.3%*
- *Higher HRSD scores* post-ECT associated with higher rate of relapse *likelihood ratio = 10.21, P=0.001*

Sackeim et al. A prospective, randomized, double-blind comparison of BL and RUL ECT at different stimulus intensities. *Arch Gen Psychiatry* 2000;57(5):425-34.

Medication Resistance *Does Not Predict* Relapse



Jelovac et al (2013). Relapse following successful ECT for major depression: a meta-analysis. *Neuropsychopharmacology* 38, 12, 2467-74.

N=61

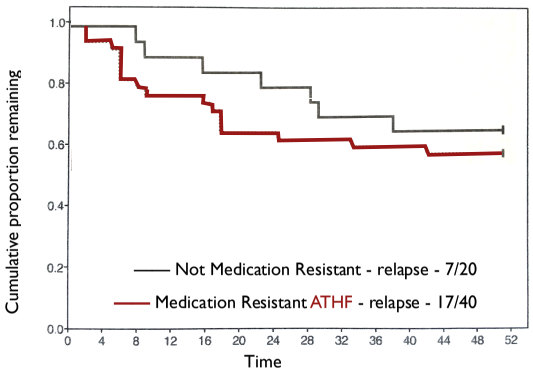
Remitters EFFECT-DEP BT vs RUL

1 year naturalistic follow-up

39% relapse

Treatment resistance

does not predict relapse



Jelovac et al. Relapse following BT and high-dose RUL ECT for major depression. Acta Psychiatr Scand. 2021;144:218-229.

Overgeneral autobiographical memory

predictors

- inability to retrieve specific memories
- cognitive *vulnerability factor* for development of depression
- more OGM predicts poor outcome *non-ECT-literature*
- few ECT-studies, conflicting results
  - did *not* predict relapse *Jelovac et al 2016*
  - *predicted* incipient relapse in 1st week after ECT *Raes et al 2008*

Jelovac et al. Autobiographical Memory Specificity in Major Depression Treated With ECT. J ECT. 2016;32:38-43
Raes et al. Overgeneral memory predicts stability of short-term outcome of ECT for depression. J ECT. 2008;24:81–83..

Risk factors for relapse-recurrence

meta-synthesis

NO ECT

- strong evidence
- increased risk
  - *history of childhood maltreatment*
  - *history of recurrence*
  - *residual depressive symptoms at the end of treatment*

Buckman et al. Risk factors for relapse and recurrence of depression in adults and how they operate: A four-phase systematic review and meta-synthesis. Clin Psychol Rev. 2018;64:13-38.

Relapse after AD

predictors / STAR*D

NO ECT

- QIDS-SR16
  - restlessness *HR=1.197, p=0.018*
  - hypersomnia *HR=1.190, p=0.009*
  - weight change *HR=1.127, p=0.041*

Residual symptoms

MODECT

80 responders

6 mth follow-up

39% relapse

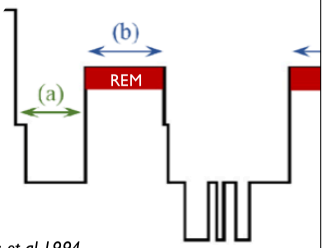
- increased risk of relapse
  - reduced sleep *MADRS*
    - *OR=2.03, 95%CI=1.11-3.69, p=0.0214*
  - lassitude *MADRS*
    - *'difficulty getting started or slowness initiating and performing everyday activities'*
    - *OR=1.62, 95%CI=1.00-2.62, p=0.0497*

Lambrichts et al. Which residual symptoms predict relapse after successful ECT for late-life depression? *submitted*

REM sleep dysregulation

predictors

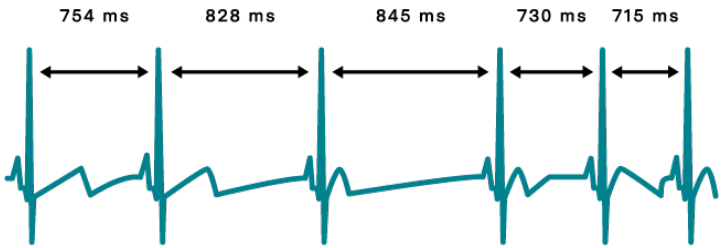
- persistence of REM sleep dysregulation during remission predicts relapse *Palagini et al 2013*
  - *shortened REM latency* (a)
  - *increased REM sleep duration* (b)
- post ECT
  - *shortened REM latency* predicts 6 mth relapse *Grunhaus et al 1994*



Palagini et al. REM sleep dysregulation in depression: state of the art. Sleep Med Rev. 2013;17:377-390
Grunhaus et al. Shortened REM latency Post ECT is associated with rapid recurrence of depressive symptomatology. Biol Psychiatry. 1994;36:214-222..

Heart rate variability

fluctuations in length of interbeat intervals typical for the normal cardiac rhythm

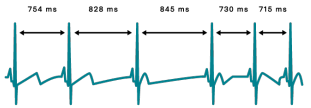


Karpyak et al. Changes in heart rate variability in response to treatment with ECT. J ECT. 2004;20:81-88.

Heart rate variability

Predictors

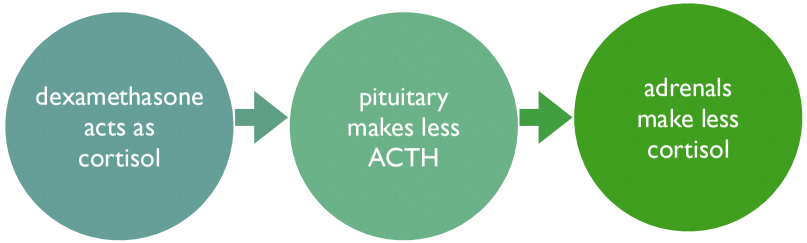
- Lower HRV - MDD higher severity, longer duration
- Increases in HRV - positive response to AD, CBT
- Decrease in HRV - non-response
- Low baseline HRV - *rapid relapse* of depression *after ECT*



Karpyak et al. Changes in heart rate variability in response to treatment with ECT. J ECT. 2004;20:81-88.

Dexamethason Suppression Test

predictors



- dexamethasone suppresses cortisol secretion
- not in *'non-suppressors'*

Dexamethason Suppression Test

predictors

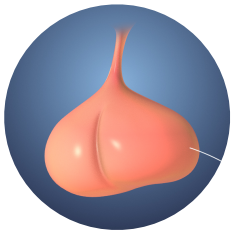
- Persistent *non-suppression* of cortisol on DST after treatment is associated with high risk of early relapse
  - ECT - *inconsistent* results
  - No well-designed studies in ECT

Ribeiro et al. The DST as a predictor of outcome in depression: a meta-analysis. Am J Psychiatry. 1993;150:1618-1629.

Thyrotropin-releasing Hormone Test

predictors

- Thyrotropin-releasing Hormone Test
  - TRH stimulates production of TSH
  - *blunted TSH-response* to TRH predicts relapse
  - few studies, *inconsistent* results



Bourgon & Kellner. Relapse of depression after ECT: a review. J ECT. 2000;16:19-31.

Which way to go…

relapse prevention

- Antidepressants
- Lithium + Antidepressants
- Lithium
- Psychotherapy
- Neurostimulation
- Continuation & Maintenance ECT

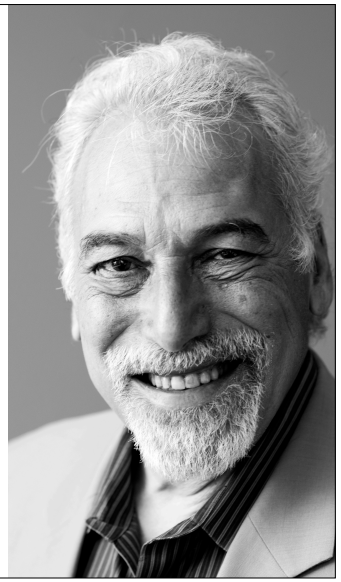
Sackeim et al. Continuation Pharmacotherapy in the Prevention of Relapse Following ECT. *JAMA* 2001.

159 remitters (54%)

N=84

Placebo, N=29	Nortriptyline, N=27 75-125 ng/mL	Nortriptyline + Lithium N=28 0.5-0.9 mEq/L
6 M Relapse		
84%	60%	39%

Most relapse in NT-Li group occurred in the first 5 weeks!



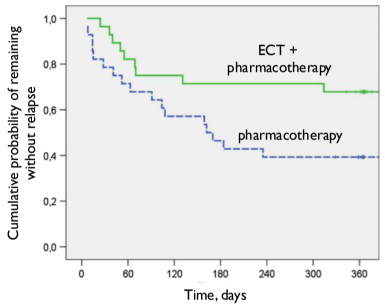
Kellner et al. Continuation ECT vs pharmacotherapy for relapse prevention in major depression: a multisite study from CORE. *Arch Gen Psychiatry* 2006, 63, 1337-1344.

Unipolar, Ham ≥ 21, 30% delusional
Median 8 R / 64% - 87% Remitters
Delusional 94% / Non-delusional 83%

N=184

Nortriptyline + Lithium N=95	0.53	C-ECT, N=89
6 M Relapse		
32% 6.8 weeks		37% 8.9 weeks

Uni/Bipolar EC-responders
MADRS <15 + at least much-improved PGI

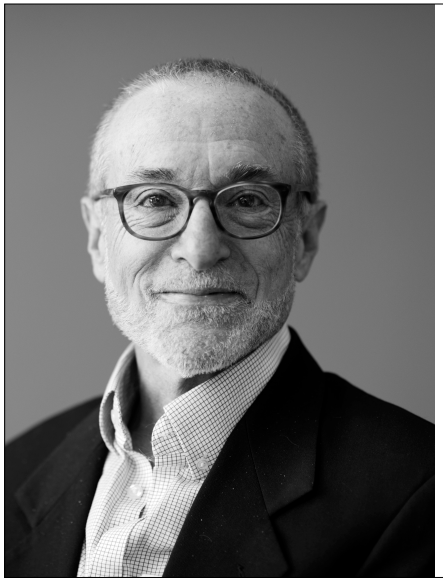


N=56

C-ECT + MEDS	MEDS
12 M	
32%	61%

Relapse = MADRS≥20 / Inpatient / Suicide

Nordenskjold et al. C-ECT with pharmacotherapy versus pharmacotherapy alone for prevention of relapse of depression: a randomized controlled trial. J ECT 2013; 29: 86-92



Prolonging Remission in Depressed Elderly *PRIDE*

Unipolar, HDRS ≥ 21, elderly
UB RUL 3/W + venlafaxine

Remission - 141/234 (60%)

Symptom-Titrated Algorithm-Based Longitudinal ECT (STABLE)

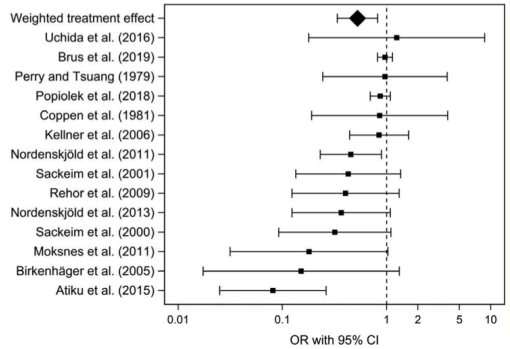
N=120
24 W

4 weekly ECT + STABLE C-ECT + Venlafaxine + Lithium	Venlafaxine + Lithium
Mean HDRS 5.5 Relapse 13% (8/61)	OR 1.7
	Mean HDRS 9.4 Relapse 20% (12/59)

Kellner et al. A Novel Strategy for Continuation ECT in Geriatric Depression: Phase 2 of the PRIDE Study. Am J Psychiatry. 2016;173:1110-1118.

Lithium may have superior efficacy in reducing relapse
after successful ECT for MD - meta-analysis

- 14 studies - 9748 participants
  - cont-treatment incl. Li N = 1571
  - without lithium N = 8177
- lithium - less likely to relapse *OR=0.53, 95% CI=0.34, 0.82*
  - NNT = 7 *95% CI=4, 21*
- older patients may benefit more from cont-treatment with lithium
- quality of evidence very low



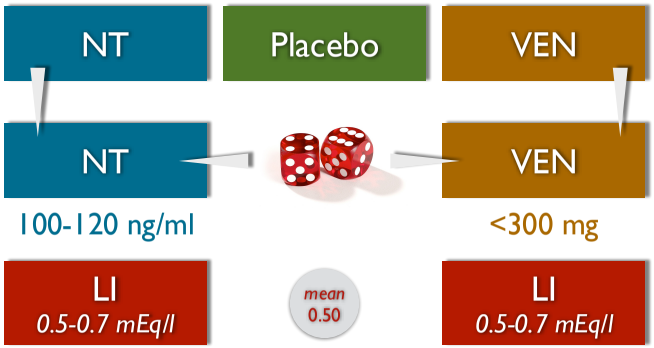
Lambrichts S, Detraux J, Vansteelandt K, Nordenskjold A, Obbels J, Schrijvers D, Sienaert P. Does lithium prevent relapse following successful electroconvulsive therapy for major depression? A systematic review and meta-analysis. Acta Psychiatr Scand 2021.

Does co-administration of antidepressants *during ECT* prevents early relapse?

OPT-ECT

phase 2

N=122 (of 181 remitters of acute phase)



Prudic et al. Pharmacological Strategies in the Prevention of Relapse After ECT. *J ECT* 2013

Antidepressants during ECT

do not prevent relapse

- overall relapse 50% / 6 m
- Early start of AD has no effect on post-ECT relapse
- NT-Li = VEN-Li

Prudic et al. (2013). Pharmacological Strategies in the Prevention of Relapse After ECT. *J ECT* 29, 3.

Psychotherapy

- augmenting ECT with psychotherapy received limited attention
- scientific rationales
  - *CBT and IPT prolong remission*
  - *neuroimaging suggests that ECT and psychotherapy have distinct mechanisms of action that may result in specific treatment effects*

McClintock et al. A systematic review of the combined use of ECT and psychotherapy for depression. J ECT. 2011;27:236-243.

Psychotherapy

Author, year	N	Intervention	Follow-up	Relapse rate	
Fenton et al 2006	6	individual CBT 12 weeks + M-ECT (average 7.6 sessions)	9 m	0%	5/6 (very) much improved compared to post-index ECT
Brakemeier et al 2014	60	manualized group CBT 15 weeks + M-Med vs M-ECT + M-Med vs M-Med	12 m	35%	
Wilkinson et al 2017	15	computer assisted CBT 2 m	6 m	33%	
Cartsens et al 2021	14	manualized group CBT 15 weeks		NA	Post-ECT symptom reduction maintained + tendency toward further decrease depression severity.

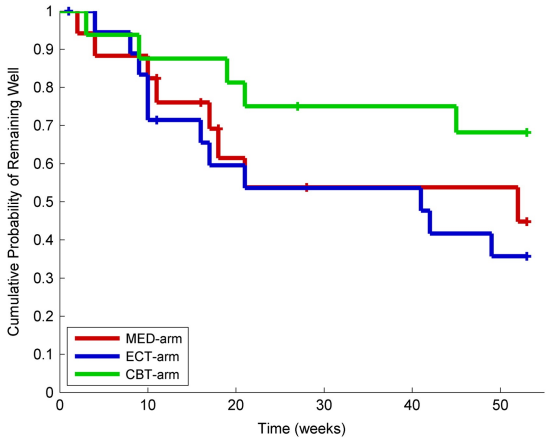
Brakemeier et al (2014). CBT as continuation treatment to sustain response after ECT in depression: a randomized controlled trial. *Biol Psychiatry* 76(3),194-202.

Unipolar, age 18-85, HRSD-24>18
Responders (70%, 63/90) after UBP RUL ECT

N=60

manualized CBT - *15 study contacts*
96% at least 1 AD
(SNRI 37.5% - SSRI 29.2% - TCA 12.5%)
28% 2nd AD - AP 40% - MS 12%

C-MED + C-CBT N=17	C-MED + C-ECT N=25	C-MED N=18
	6 *m continuation treatment*	
23% N=17	60% N=18	56% N=15
relapse	12 *m*	
35% N=16	72% N=18	67% N=14



Brakemeier et al (2014). CBT as continuation treatment to sustain response after ECT in depression: a randomized controlled trial. *Biol Psychiatry* 76(3),194-202.

'group CBT in combination with AD might be an effective continuation treatment to sustain response after successful ECT in MDD patients'

Eva-Lotta Brakemeier 2014

C-ECT + C-Med does worse then C-Med > reason?
confounders?
propofol ?
RUL non-responders (switched to BT) received RUL M-ECT
ultrabrief pulse width?

Youssef NA, McCall WV. Continuation antidepressant strategies after electroconvulsive therapy: ultrabrief pulse versus cognitive-behavioral therapy. Biol Psychiatry. 2015;77:e7.

Psychotherapy

Author, year	N	Intervention	Follow-up	Relapse rate	
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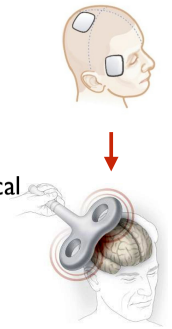
Wilkinson et al 2017	15	computer assisted CBT 9 lessons over 2 m	6 m	33%	
Cartsens et al 2021	14	manualized group CBT 15 weeks		NA	benefit maintained + tendency toward further decrease depression severity.

M-TMS

as a substitute for successful M-ECT

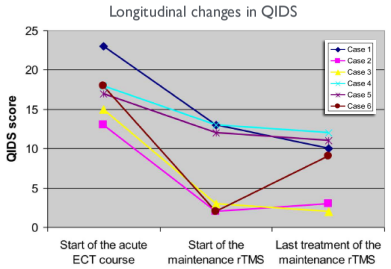
- N=6 - M-ECT
- switch *cognitive side-effects, preference, stigma*
- TMS 1/3.5W
- all patients maintained or improved clinical status @ 3 & 6 months
- 2 relapsed @ 8 & 9 months



Cristancho et al. TMS maintenance as a substitute for m-ECT: a case series. *J ECT* 2013, 29(2), 106-8.

M-TMS

after successful ECT



- N=6
- bilateral TMS 1-2/W
- 5/6 maintained response status from 6-13 months

Noda et al. rTMS to maintain treatment response to ECT in depression: a case series. *Frontiers in psychiatry* 2013, 4, 73

Case Maria G

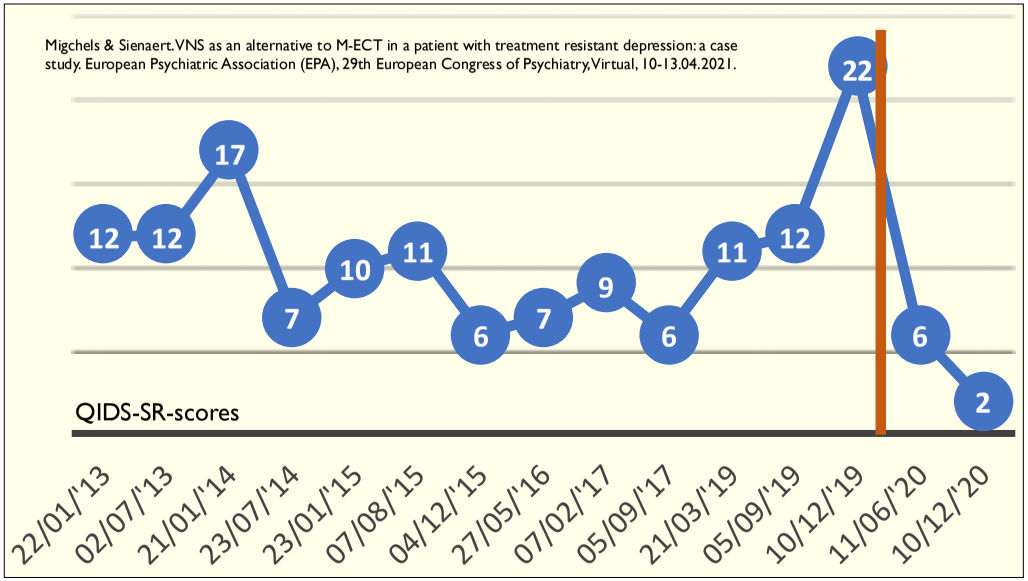
Vagal Nerve Stimulation

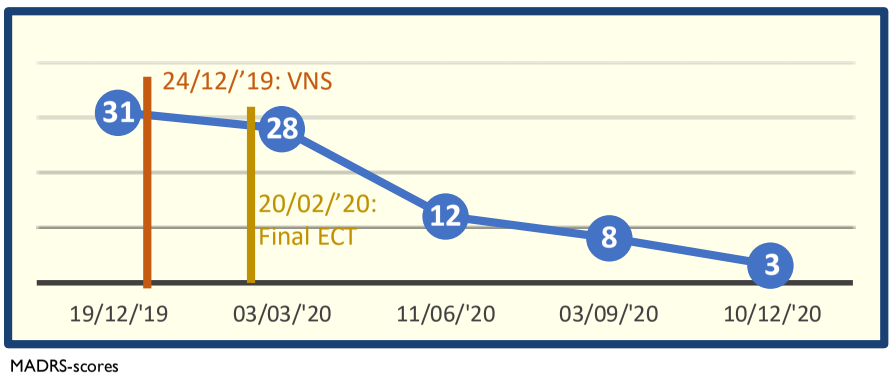
- 60 yr
- chronic depression; double depression*>1999*
- 2 SSRI, 2 SNRI, Lithium, Quetiapine, Agomelatine, Maprotiline, Trazodone, Mianserine, Lamotrigine

VNS

120 M-ECT - STOP 02.20 *stopped abruptly 2mth after device implant (pandemic).*

2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020

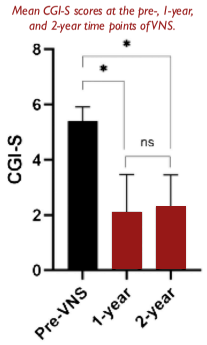




VNS

as M-ECT-substitute

- N=10 *unipolar / bipolar*
- 1.9 M-ECT / month *year before VNS*
  - M-ECT stop in 8 patients *2nd year after VNS*
  - no additional acute ECT
- marked reduction in CGI-S scores >



Aaronson et al. VNS in Patients Receiving Maintenance Therapy With ECT: A Series of 10 Cases. J ECT. 2021;37:84-87.

There are many unanswered questions about the optimal treatment of depressed patients following response to ECT.

Rather than advocating a specific class of antidepressant medication for continuation therapy,
it seems more prudent to maintain a flexible approach
to management that takes into account the type and adequacy of previous treatment.

Flint A. The impact of treatment resistance on depressive relapse following ECT. Acta Psychiatr Scand 1997;96:405-406.

- Without continuation treatment, early relapse is high
- Maintenance treatment significantly reduces relapse
- Possible predictors - *conflicting results*
  - younger patients
  - *absence of psychotic symptoms*