Clinical and biological effects of different stimulation techniques

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NACT: ECT – optimizing treatment and preventing relapse

Disclosures: funded by the Health Research Board, Ireland
1. Electrode placement
2. Pulse width
3. Preventing relapse
4. The EFFECT-Dep Trial
   (Electrode placement revisited)
1. Electrode placement

- Laterality
- Waveform
- Pulse width
- Stimulus intensity

Bitemporal

Right unilateral

Bifrontal
Conclusions

Increasing the electrical dosage increases the efficacy of right unilateral electroconvulsive therapy, although not to the level of bilateral therapy.

High electrical dosage is associated with a more rapid response, and unilateral treatment is associated with less severe cognitive side effects after treatment.
Systematic review and meta-analysis of bifrontal ECT versus bitemporal and unilateral ECT for depression

BT vs BF ECT: no significant difference in depression rating (HDRS)
RUL vs BF ECT: no significant difference in depression rating (HDRS)
Global cognition (MMSE): slight advantage for BF over BT ECT but not over RUL ECT.
Cognition: insufficient data to recommend BT ECT.
Conclusion #1

There appears to be no particular major advantage to Bifrontal ECT compared to Bitemporal or high-dose RUL ECT.

Maybe less cardiac effects?

DRAW YOUR OWN CONCLUSIONS!!!
2. Ultrabrief pulse ECT

- Shortening pulse widths
- Ultrabrief: <0.5ms
- Increasingly used
  - 26% of Dutch clinics in 2009
- Efficacy unclear
Few RCTs
Heterogeneity ++
Very variable outcomes; 6-77% remission rates in RCTs!
Efficacy and cognitive side effects after brief pulse and ultrabrief pulse right unilateral electroconvulsive therapy for major depression: a randomized, double-blind, controlled study.

Spaans HP¹, Verwijk E, Comijs HC, Kok RM, Sienaert P, Bouckaert F, Fannes K, Vandepoel K, Scherder EJ, Stek ML, Kho KH.

**RESULTS:**

- ITT remission rates: BP 50% (29/58) vs UBP 41.4% (24/58) (P = .039)
- Completer remission rates: BP 68.4% (26/38) vs UBP 49.0% (24/49) (P = .019)
- Fewer treatment sessions to achieve remission: 7.1 (2.6) vs 9.2 (2.3) (P = .008).
- No significant group differences for cognitive assessments (retrograde amnesia, semantic memory, and lexical memory)

8 x ST in both groups; high drop-out in BP group
ECS Study #1: Sham vs Brief-pulse vs Ultrabrief-pulse

A comparison of brief pulse and ultrabrief pulse electroconvulsive stimulation on rodent brain and behaviour

Sinead O'Donovan a,b, Mark Kennedy a, Blaithin Guinan a, Shane O'Mara a, Declan M. McLoughlin a,b,*

Progress in Neuro-Psychopharmacology & Biological Psychiatry 37 (2012) 147-152
**ECS: Sham vs Brief-pulse vs Ultrabrief-pulse**

**Behavioural antidepressant effect – Forced swim test**

n=6 per group, *p<0.05 compared to control group.

**Seizure durations: no differences**

O’Donovan et al (2012)
BDNF protein levels in the hippocampus following ECS

n=6 per group, *p<0.05, **p<0.01 compared to control and UBP groups.
Hippocampal “neurogenesis”

Cell proliferation following ECS. BP treatment significantly increased the relative number of BrdU-labelled cells in the dentate gyrus compared to sham-treated control animals (p<0.05)
ECS study #2: Sham vs Brief-pulse vs Ultrabrief-pulse in the cortisol model of depression
**Behaviour: Forced Swim Test**
N=11-14/group

**Molecular: BDNF**
N=11-14/group
Conclusion #2

Ultrabrief pulse ECT: confusion reigns!

• Optimal parameters not yet identified

• Probably requires high stimulus dose but then may not be able to maintain 0.3 msec pulse width

• Not for routine use

• Experimental for now
3. Relapse rates

6 months

(a) **34.0%** (95% CI=27.2-41.5%, I²=76%) of patients (N=844) treated with continuation pharmacotherapy relapsed.

NB: historical trend effects

(b) post DSM-III era (N=710): **37.7%** (95% CI=30.7-45.2%, I²=70%)

• No effect of tx resistance (p=0.43)

• Lower relapse with:
  - Psychosis (p=0.004)
  - Age (p=0.04)

Jelovac et al (2013) *Neuropsychopharmacology*
Relapse rates: (a) 3, (b) 12 and (c) 24 months

3 months
27.1% of patients (N=350) on continuation pharmacotherapy had relapsed (95% CI=20.5-34.8%, $I^2=48%$)

12 months
51.1% (95% CI=44.7-57.4%, $I^2=27%$) (N=348)

24 months
50.4% (95% CI=41.2-59.6%, $I^2=0$) (N=111)
Relapse rates with continuation ECT

6-months

37.2% (95% CI=23.4-53.5%, I²=57%), four eligible C-ECT samples (N=146), i.e. same as modern-era AD-treated patients (37.7%).

39.5% (95% CI=31.9-47.7%, I²=81%) for any form of recognised continuation therapy across 19 eligible studies (N=1001).

45.4% (95% CI=35.2-55.9%, I²=0), two studies of C-ECT only (N=86).
Relapse rates in untreated samples

Unmedicated patients

- 3 months
  - 47.9% (95% CI=38.1-57.9%, I²=0); two studies (1973).

Placebo-treated samples

- 3 months
  - 62.7% (95% CI=47.6-75.8%, I²=0); three RCTs (1996-2010)

- 6 months
  - 65.5% (95% CI=49.7-78.5%, I²=72%); seven RCTs (1965-2006)
  - 78.0% (95% CI=66.1-86.5%, I²=0); four RCTs (N=65) (1984-2006)
Relative risk of relapse on continuation antidepressants vs. placebo

3 months
Any AD vs placebo; 3 studies
RR=0.56 (95% CI=0.38-0.81, p=0.002, NNT=3.5, I²=0)

6 months
Any AD vs placebo; 7 studies (n=402)
RR=0.49 (95% CI=0.39-0.62, p<0.0001, NNT=3.3, I²=0)
Conclusion #3

Relapse rates following ECT are high: 30% at 3 mths, 40% at 6 mths and 50% at 12 mths
  • similar to STAR*D Study which had lower remission rates
  • but don’t forget superior remission rates with ECT

• relapse rates have increased over time

• vigorous maintenance therapy required post ECT
  • not yet clear what is best
  • most studies on older TCAs
  • C-ECT to be optimised
4. The EFFECT-Dep Trial

**OBJECTIVE:** to perform a pragmatic, randomised, non-inferiority trial comparing standard bitemporal ECT (1.5 x ST) and high-dose unilateral ECT (6 x ST) in severe depression in routine practice
Background

• Global treated person (<65) rate: 2.34/10,000 population → 1.4 million per year

• Global average no. of treatments: 8 per course

• Western countries: older, female, depression
  Asian countries: younger, males, schizophrenia

• Wide variation but **bilateral** ECT is the most common form
Goal: Decrease side-effects but maintain effectiveness

RCTs of bitemporal vs high-dose RUL ECT

1. Sackeim et al (2000) *Arch Gen Psychiatry* (n=20/group)
5. Sackeim et al (2009) *Arch Gen Psychiatry* (+pharmacotx; n~45-70/group)
From: A Prospective, Randomized, Double-blind Comparison of Bilateral and Right Unilateral Electroconvulsive Therapy at Different Stimulus Intensities


- underpowered
- thrice weekly ECT
- 2.5 x ST for BT ECT → ↑ side-effects
- meds stopped x ≥5 days; lorazepam rescue

Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial†

Charles H. Kellner, Rebecca Knapp, Mustafa M. Husain, Keith Rasmussen, Shirlene Sampson, Munro Cullum, Shawn M. McClintock, Kristen G. Tobias, Celena Martino, Martina Mueller, Samuel H. Balline, Max Fink and Georgios Petratos

- 30% drop-out during tx phase
- thrice weekly ECT
- meds stopped
“He gave what little wealth he had
To build a house for fools and mad;
And show’d by one satiric touch,
No nation wanted it so much.

St Patrick’s University Hospital

Dean Jonathan Swift
(1667-1745)
A Tale of a Tub
A Modest Proposal
Gulliver’s Travels
**EFFECT-Dep Trial**

**Design:** two-group parallel-design randomised non-inferiority trial; continued on usual care. Treated at St Patrick’s University Hospital, Dublin (ECTAS-accredited).

**Randomisation:** minimisation stratification (source of referral; previous ECT; age, ≥65) with variable block sizes; just before 1st ECT session; independent & computerised - Clinical Trials Unit, IOP, KCL

**Blinding:** patients, clinicians, raters

**Inclusion:** major depressive episode (DSM-IV; SCID) referred for ECT; HDRS-24 ≥21; ≥ 18 years

**Exclusion:** unfit for general anaesthesia; ECT in previous six months; dementia or other Axis 1 diagnosis; alcohol/other substance abuse in previous six months; inability/refusal to consent.

**Ethical approval:** St Patrick’s University Hospital Research Ethics Committee
ECT

• twice weekly

• Mecta 5000M device (Mecta Corporation, USA)

• methohexitone (0.75-1.0 mg/kg) and suxamethonium (0.5-1.0 mg/kg)

• EEG monitoring

• seizure threshold (ST) was established by a method of limits at the first session and subsequent treatments given at 1.5 x ST for BT ECT and 6.0 x ST for RUL ECT

• Stimulus charge is titrated upward as required during treatment courses following a standard stimulus dosing protocol.

• number of ECTs determined by referring physicians, up to 12 sessions (as per Mental Health Commission)
Clinical outcomes

Primary: 24-item Hamilton Rating Scale for Depression (HDRS)

- baseline; after every 2 ECTs; during 12 mth follow-up
- **Response**: ≥60% decrease in HDRS from baseline and score ≤16

- **Remission**: ≥60% decrease in HDRS from baseline and score ≤10 on two occasions separated by one week

- **Relapse**: ≥10 point increase in HDRS compared to end-of-treatment score plus HDRS ≥16; increase in the HDRS should be maintained two weeks later. Hospital admission, further ECT, and deliberate self-harm/suicide also constitute relapse.
Sample size estimation & clinical significance

In a large series (n = 253) of depressed patients, Petrides et al. (2001) found a mean (SD) reduction in 24-item HDRS of 25.6 (9.4) after treatment with BT ECT (1.5 x ST).

We estimated that:

- **69 patients** required per treatment group
- to have **80% power**
- to demonstrate, using a one-sided equivalence t-test at **5% level**
- that mean reduction in 24-item HDRS achieved using high-dose RUL ECT is **no more than 4 points** (i.e. equivalent to 3 points on 17-item HDRS) less than that achieved using standard BT ECT, assuming a common within-group SD of change scores of 9.4 and equal expected group mean change scores.
Statistical inferential analyses

- Intention to treat
- Single primary experimental hypothesis
- No planned subgroup analyses
- No planned interim analysis
- Statistician blinded
- Linear mixed models for HDRS
- Multiple imputation for missing data

Enrollment

475 Assessed for eligibility

335 Excluded
- 35 Involuntary status
- 32 Already in trial
- 29 HRSD score <21
- 29 Voluntary but lacked capacity
- 28 ECT in last 6 months
- 24 Other Axis 1 disorder
- 15 Substance abuse in last 6 months
- 12 Cognitive impairment
- 11 Did not meet SCID criteria
- 7 Referred to specific laterality

103 Refused
- 5 Treating team refused
- 5 Referred late

140 randomised

70 allocated to bitemporal ECT
70 completed allocated intervention

1 excluded from trial post-randomisation (altered diagnosis)

10 stopped 6 month follow-up
- 7 withdrew consent
- 2 Unable to contact
- 1 died

69 included in intention to treat analysis

70 allocated to right unilateral ECT
70 completed allocated intervention

1 excluded from trial post-randomisation (pre-existing neurological disorder)

6 stopped 6 month follow-up
- 3 withdrew consent
- 3 Unable to contact

69 included in intention to treat analysis
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total sample (n=138)</th>
<th>Right Unilateral (n=69)</th>
<th>Bitemporal (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>56.7 (14.3)</td>
<td>56.6 (15.3)</td>
<td>56.8 (14.4)</td>
</tr>
<tr>
<td>Gender, female (%)</td>
<td>07(63.0%)</td>
<td>40(58.0%)</td>
<td>47(68.1%)</td>
</tr>
<tr>
<td>Education: years</td>
<td>13.1(3.4)</td>
<td>13.7(3.0)</td>
<td>12.6(3.8)</td>
</tr>
<tr>
<td>Socio-economic group (1-5)</td>
<td>3.1(1.4)</td>
<td>2.9(1.3)</td>
<td>3.3(1.5)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>76(55.9%)</td>
<td>38(56.7%)</td>
<td>38(55.1%)</td>
</tr>
<tr>
<td>Single</td>
<td>35(25.7%)</td>
<td>17(25.4%)</td>
<td>18(26.1%)</td>
</tr>
<tr>
<td>Widowed/divorced</td>
<td>25(18.1%)</td>
<td>12(17.9%)</td>
<td>13(18.8%)</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar depression</td>
<td>32(23.2%)</td>
<td>16(23.2%)</td>
<td>16(23.2%)</td>
</tr>
<tr>
<td>Presence of psychosis</td>
<td>29(21.0%)</td>
<td>16(23.2%)</td>
<td>13(18.8%)</td>
</tr>
<tr>
<td>Treatment resistance</td>
<td>98(71.0%)</td>
<td>45(65.2%)</td>
<td>53(76.8%)</td>
</tr>
<tr>
<td>History of previous ECT</td>
<td>53(38.4%)</td>
<td>26(37.7%)</td>
<td>27(39.1%)</td>
</tr>
<tr>
<td>Episode duration: weeks</td>
<td>31.6(52.0)</td>
<td>26.7(51.0)</td>
<td>36.7(66.9)</td>
</tr>
<tr>
<td>Number of previous episodes</td>
<td>5.3(4.5)</td>
<td>5.7(4.8)</td>
<td>5.1(4.4)</td>
</tr>
<tr>
<td>HRSD-24 baseline</td>
<td>29.9(6.2)</td>
<td>30.4(6.1)</td>
<td>29.5(6.3)</td>
</tr>
<tr>
<td>MMSE baseline</td>
<td>27.7(2.1)</td>
<td>28(1.8)</td>
<td>27.4(2.4)</td>
</tr>
<tr>
<td>NART</td>
<td>103.5(6.6)</td>
<td>109.2(5.6)</td>
<td>107.4(7.8)</td>
</tr>
<tr>
<td>CGI-5 baseline</td>
<td>5.3(0.7)</td>
<td>5.4(0.7)</td>
<td>5.3(0.7)</td>
</tr>
<tr>
<td><strong>Psychotropic medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of psychotropics</td>
<td>4.2(1.4)</td>
<td>4.3(1.3)</td>
<td>4.2(1.5)</td>
</tr>
<tr>
<td>SSRI</td>
<td>29</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>SNRI</td>
<td>67</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>39</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Tetracyclic antidepressants</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>46</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Agomelatine</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lithium</td>
<td>56</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Anticonvulsants*</td>
<td>39</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>81</td>
<td>35</td>
<td>46</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>97</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>2-hypnotic</td>
<td>69</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bupropion</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MAO-I</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Buspirone</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are mean (SD) or n (%), unless otherwise indicated. Treatment resistance was based on the Antidepressant Treatment History Form. HRSD-24: 24-item Hamilton Rating Scale for Depression. MMSE: Mini Mental State Examination. NART: National Adult Reading Test. CGI-S: Clinical Global Assessment of Severity Scale. SSRI: Selective serotonin reuptake inhibitor. SNRI: Serotonin and Noradrenaline Reuptake Inhibitor. *Anticonvulsants include Lamotrigine, Sodium Valproate and Pregabalin prescribed as mood stabilizers or anxiolytic.

*Table 1: Baseline characteristics*
Mean HDRS estimated to be 1.2 points higher in the Bitemporal group; 95% CI, -1.510 to 3.995, i.e. within the non-inferiority threshold.
### Remission following course of ECT

<table>
<thead>
<tr>
<th>Electrode Placement</th>
<th>Achieved remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (Unilateral)</td>
<td>30</td>
</tr>
<tr>
<td>No (Bitemporal)</td>
<td>40</td>
</tr>
</tbody>
</table>

### Response to ECT

<table>
<thead>
<tr>
<th>Electrode Placement</th>
<th>Achieved responder status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (Unilateral)</td>
<td>35</td>
</tr>
<tr>
<td>No (Bitemporal)</td>
<td>29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Whole group</th>
<th>RUL ECT</th>
<th>BT ECT</th>
<th>Fisher’s exact test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>61/138 (44.2%)</td>
<td>32/69 (46.4%)</td>
<td>29/69 (42.0%)</td>
<td>P=0.30</td>
</tr>
<tr>
<td>Response</td>
<td>77/138 (55.8%)</td>
<td>42/69 (60.9%)</td>
<td>35/69 (50.7%)</td>
<td>P=0.70</td>
</tr>
</tbody>
</table>
Overall 6 month relapse rate for remitters was 31% 25% (RUL) vs 38% (BT)

Case Processing Summary

<table>
<thead>
<tr>
<th>Electrode Placement</th>
<th>Remitters</th>
<th>Relapses</th>
<th>Censored (did not relapse)</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>32</td>
<td>8</td>
<td></td>
<td>24</td>
<td>75.0%</td>
</tr>
<tr>
<td>Bitemporal</td>
<td>29</td>
<td>11</td>
<td></td>
<td>18</td>
<td>62.1%</td>
</tr>
<tr>
<td>Overall</td>
<td>61</td>
<td>19</td>
<td></td>
<td>42</td>
<td>68.9%</td>
</tr>
</tbody>
</table>

Overall Comparisons

<table>
<thead>
<tr>
<th>Overall Comparisons</th>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>1.723</td>
<td>1</td>
<td>.189</td>
</tr>
</tbody>
</table>

Test of equality of survival distributions for the different levels of Electrode Placement.
Subjective cognitive complaints:
less with RUL ECT

<table>
<thead>
<tr>
<th></th>
<th>Predicted mean* RUL (n=69)</th>
<th>Predicted mean* Bitemporal (n=69)</th>
<th>Comparison of randomisation groups**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Estimated difference in means (95% CI) BT - RUL</td>
</tr>
<tr>
<td>Total side effects: CSSES total score***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (sample average)</td>
<td>22.42 (n=50)</td>
<td>22.42 (n=48)</td>
<td>1.22 (0.93 to 1.60)</td>
</tr>
<tr>
<td>EOT</td>
<td>14.15 (n=63)</td>
<td>17.25 (n=62)</td>
<td>1.08 (0.73 to 1.58)</td>
</tr>
<tr>
<td>3 Months</td>
<td>12.45 (n=47)</td>
<td>13.40 (n=32)</td>
<td>1.39 (0.90 to 2.13)</td>
</tr>
<tr>
<td>6 Months</td>
<td>8.72 (n=39)</td>
<td>12.09 (n=38)</td>
<td></td>
</tr>
<tr>
<td>Cognitive side effects: CSSES cognitive score***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (sample average)</td>
<td>5.0 (n=52)</td>
<td>5.0 (n=48)</td>
<td>1.44 (1.06 to 1.96)</td>
</tr>
<tr>
<td>EOT</td>
<td>3.80 (n=63)</td>
<td>5.48 (n=62)</td>
<td>1.15 (0.82 to 1.61)</td>
</tr>
<tr>
<td>3 Months</td>
<td>4.21 (n=47)</td>
<td>4.86 (n=32)</td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td>3.28 (n=39)</td>
<td>4.91 (n=38)</td>
<td>1.50 (1.05 to 2.13)</td>
</tr>
</tbody>
</table>

* Means are predicted for patients with average baseline outcome value, who are of younger age (≤65 years), referred from St. Patrick’s and have no previous experience of ECT. **All analyses were carried out using multiple imputation with 200 imputations (see Statistical Analysis). *** Analysis carried out on the log-scale, means backtransformed and effect estimates representing factor changes, MMSE: Mini-Mental State Examination TMT: Trail Making Test (versions A and B); FCSRT: Free and Cued Selective Reminding Test; CFT: Complex Figure Test.
Conclusion #4

- RUL ECT (6xST) is not inferior to standard BT ECT (1.5xST)
- RUL ECT (6xST) has cognitive advantages
- RUL ECT (6xST) should be the first-line form of ECT for depression
Aitäh!

**EFFECT-Dep Trial**
Maria Semkovska
Martha Noone
Ana Jelovac
Ross Dunne
Adam Kavanagh
Eric Kolshus
Sabine Landau (IOP, KCL)
Mary Carton
Diarmaid O’Lonergan
Sinead Lambe
Caroline McHugh

**ECT Relapse meta-analysis**
Ana Jelovac, Erik Kolshus

**Bifrontal meta-analysis**
Ross Dunne

**Biomarker & pre-clinical studies**
Karen Ryan
Sinead O’Donovan
Victoria Dalton
Nino Glaviano