ECT: Learning From Recent Trials

Charles H. Kellner, MD
Professor, Department of Psychiatry
Icahn School of Medicine at Mount Sinai

ISCTM
Philadelphia, PA
27 September, 2016
Disclosures

NIMH (grant support)

UpTo Date (honoraria for writing ECT sections)

Cambridge University Press Royalties

Northwell Health System (honoraria for teaching ECT course)

Psychiatric Times (honoraria for writing ECT sections)
Antidepressant Treatment Remission Rates

ECT

Percent Remitted

rTMS

Pharma

ECT

Antidepressant Treatment

rTMS (Sham-controlled RCT) n=92
rTMS (Open label) n=100
dTMS n=233
Citalopram n=4,041
Ketamine n=47
ECT n=531
ECT/Psychotic Dep n=77

ECT 83

Pharma 64

rTMS 36

Citalopram 33

dTMS 30

rTMS (Open label) 25

rTMS (Sham-controlled RCT) 14
Treatments for Depression

Psychotherapy → Antidepressant Medication → ECT

Severity:
- Mild
- Moderate
- Severe
ECT’s Shortcomings

• Medical risks (safety)
  – risk of general anesthesia (death in 1/10,000)

• Cognitive effects (tolerability)
  – retrograde amnesia

• Does not prevent future episodes (unless use maintenance ECT)

• Post-ECT relapse rates higher in the modern era
ECT Evidence Base

• What we know about ECT:
  – >15,000 PubMed citations
  – Efficacy in specific diagnoses
  – Overall safety

• What we don’t know about ECT
  – Optimal treatment technique
  – Prediction of cognitive effects for a specific patient
  – Optimal post-ECT maintenance strategies
  – Exact mechanism of action
Methodological Issues: Generic

• Placebo unethical in such sick patients
• Power always an issue
  – sample sizes are limited by patient population and cost
• Replication rarely done
  – bench-to-bedside occurs TOO quickly
• Statistical analyses need to be done at “arm’s length”
Methodological Issues

• ECT vs other antidepressant treatments
  – rTMS, DBS, TDCS
  – Ketamine (large PCORI trial)
  – new antidepressant medications

• ECT plus antidepressant medication

• ECT vs other types of ECT
  – Electrode placements
  – Stimulus types
  – Escalation from “weaker” to “stronger” ECT
  – Optimizing anesthesia technique
Methodological Issues

• Cognition studies
  – Memory extraordinarily hard to study
  – Retrograde amnesia particularly hard to study
  – Cognition-sparing medications inadequately studied

• Mechanism of action studies
  – Large scale neuroimaging studies underway
CORE I: Continuation ECT vs Pharmacotherapy

Phase I

ECT

- Unipolar major depression
- Baseline HAM-D_{24} ≥ 21
- 3x/week bilateral

Randomize

Phase II

Nortriptyline + Lithium

Continuation ECT
Remitter Status for Patients Entering Phase I and for Patients Completing Phase I (N=530)

Kellner CH, et al., Arch Gen Psychiatry. 2006 Dec;63(12):1337-44.
CORE I: Relapse Status at 6 Months

Kellner CH, et al., Arch Gen Psychiatry. 2006 Dec;63(12):1337-44.
**CORE II: Three Electrode Placement**

- **ECT**

  - **HAM-D_{24}**
    - (acute phase: 3x/week)
  - **Neuropsych. battery**

  - **Randomize**

  - **Unipolar or Bipolar Major Depression**
  - **Baseline HAM-D_{24} ≥ 21**
  - **3x/week**

  - **Baseline**
  - **Post ECT #4**
  - **Acute Phase End**
  - **1 Week Follow-up**
  - **2 Months Follow-up**
CORE II: Remission Outcome by EP

Prolonging Remission in Depressed Elderly (PRIDE)

PHASE I

RUL UBP ECT + VLF

- Week 1
- Week 2
- Week 3
- Week 4

~1 month

PHASE II

Randomize Remitters

STABLE+

4 ECT + Flex ECT + VLF + Li

PHARM

VLF + Li

6 months
# PRIDE Phase I

<table>
<thead>
<tr>
<th>Week</th>
<th>ECT</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>n = 240</th>
</tr>
</thead>
</table>

- **ECT**

1. **1 month**
2. **6 months**

- **RUL UBP ECT + VLF**

- **STABLE**
- **VLF + Li**
PRIDE Selection Criteria

• Inclusion
  - ≥60 yr, MDE, Unipolar (MINI)
  - Baseline HRSD≥21 (24-item)
  - ECT clinically indicated, competent to give consent

• Exclusion
  - bipolar disorder, schizophrenia, schizoaffective disorder, mental retardation
  - delirium, dementia, or substance abuse/dependence in past 6 months
  - general medical condition or CNS disease that may affect cognition or response to treatment.
  - medical condition contraindicating Li or VLF
  - Failure to respond to adequate trial of Li + VLF, or ECT, in the current episode, or history of intolerance to Li or VLF.
PRIDE ECT Procedures

- Dose Titration (5, 10, 15, 20 %)
- 6x Seizure Threshold RUL (0.25 ms) ECT 3/wk
- Anesthesia
  - Glycopyrrolate (0.2 mg IV) (first procedure only)
  - Methohexital (0.75 mg/kg)
  - Succinylcholine (0.75 mg/kg)
- Adequate seizure ≥15s motor
- Midcourse dose increase if response plateaus
Eligible for Baseline Assessment
N=786

Not Eligible to begin Phase 1
N=34

Eligible to begin Phase 1
N=245

Began Phase 1
N=240

Completed Phase 1
N=172

Early Termination Phase 1
N=68

Phase 1 Nonremitters
N=24

Phase 1 Remitters
N=148

Randomized Phase 2
PRIDE Phase I Remission$^1$ and Response Proportions$^2$

- **Remission**: Last two HRSD$_{24}$ ≤ 10
- **Response**: ≥ 50% decrease HRSD$_{24}$ (Baseline - Last)

<table>
<thead>
<tr>
<th>Category</th>
<th>Percent</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remitters</td>
<td>61.7%</td>
<td>148/240</td>
</tr>
<tr>
<td>Nonremitters</td>
<td>10.0%</td>
<td>24/240</td>
</tr>
<tr>
<td>Dropouts</td>
<td>27.9%</td>
<td>68/240</td>
</tr>
<tr>
<td>Responders</td>
<td>70.4%</td>
<td>169/240</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>29.6%</td>
<td>71/240</td>
</tr>
</tbody>
</table>
PRIDE Phase I: Individual Patient HRSD Trajectories for Remitters (n=148)
PRIDE Phase II

Phase I

Randomize Remitters

 месяцы: 1 2 3 4 5 6

STABLE+
ECT || || + flex ECT
VLF + Li

PHARM
VLF + Li
PRIDE Phase II Consort Chart

Randomized Phase 2
N=128

STABLE+
N=64

Did not receive treatment
N=3

Included in ITT
N=61

Completed
N=39

Early termination
N=22

PHARM
N=64

Included in ITT
N=59

Completed
N=33

Did not receive treatment
N=5

Early Termination
N=26
**PRIDE PHASE II: Longitudinal Trajectory of Modeled**

HRSD-24 Means in PHARM and STABLE+ Arms

*Model contains treatment, time, treatment-by-time with HRSD baseline, site, psychosis as adjustment covariables*

**Δ=4.2 is difference in baseline, site, psychosis adjusted least squares means for STABLE+ vs PHARM

95%CI: 1.6-6.9

p=0.002**
PRIDE Phase II Results

• At 6 month study endpoint, mean HRSD-24 score for \( \text{STABLE}^+ = 4.2 \) vs \( \text{PHARM} = 8.4 \) \( (p=0.002) \)

• CGI-S: odds of being rated “not at all ill” were 5.2 times greater for \( \text{STABLE}^+ \) vs \( \text{PHARM} \)

• Odds of relapsing 1.7 times higher for \( \text{PHARM} \) vs \( \text{STABLE}^+ \)

• 34.4% (21/61) of \( \text{STABLE}^+ \) patients received at least one additional ECT in weeks 5-24
Relapse* by Treatment Group

- Overall Relapse Rate: 16.7%
- PHARM Relapse Rate: 20.3%
- STABLE+ Relapse Rate: 13.1%

*Relapse defined as when a patient was removed from the study for safety because of worsening of MDD requiring alternative treatment (2 consecutive HRSD\textsubscript{24} ≥ 21, or patient required psychiatric hospitalization, or patient became suicidal).
The EFFECT-Dep Trial – a randomised trial of bitemporal and high-dose unilateral ECT for depression (ISRCTN23577151)

Declan McLoughlin
Dept of Psychiatry &
Trinity College Institute of Neuroscience
Trinity College Dublin
St Patrick’s University Hospital
Ireland

Disclosures: funded by the Health Research Board, Ireland
EFFECT-Dep Trial

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

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

**Blinding:** patients, clinicians, raters, statistician

**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 and patients, up to 12 sessions (as per Mental Health Commission)
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.
Primary outcome: HDRS-24

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.
**Strengths**

- real-world trial, reflecting Irish and UK practice
- good generalisability
- overall remission similar to community studies
- randomisation effective
- good retention for primary outcome
- adequately powered
- rater blinding effective

**Limitations**

- depression only
- unable to include very severe cases (~7% of pts)
- multiple imputation (but similar to complete case analyses)

**Conclusions**

- RUL ECT (6xST) is not inferior to standard BT ECT (1.5xST)
- RUL ECT has cognitive advantages
Conclusions

• ECT is the most effective and one of the most studied antidepressant treatments
• Despite this, several important issues remain inadequately researched
• Methodological challenges include recruitment, inability to use placebo and inadequate funding due to stigma