To shock or not to shock
Psychiatrisch Ziekenhuis Duffel, April 28th, 2016

Psychotic depression and ECT

Søren Dinesen Østergaard, MD, PhD
Associate Professor
Psychosis Research Unit
Aarhus University Hospital - Risskov
Email: soeoes@rm.dk
DENMARK

Trivia:
- 5.5 mio inhabitants
- 43,000 km²
- Language: Danish
- Constitutional monarchy
- Tax financed hospital service
- 3000 psychiatric beds
Agenda

• What is psychotic depression?

• Is it sensible to study *psychotic* depression specifically? (In other words: Is psychotic depression a distinct entity?)

• ECT for psychotic depression – the evidence

• (Tentative) conclusions based on current evidence

• A potential future study on ECT for psychotic depression

• Let us not ignore the measures...

• What do guidelines say and psychiatrists do?

• A representative case – ECT for psychotic depression (video)
• Conflicts of interest: None

• Disclaimer: MD, PhD (researcher physician). Not an experienced clinician.

• That being said....
ICD-10 Criteria – Psychotic Depression (Unipolar)

Core symptoms:
1. Depressed mood
2. Loss of interest or pleasure
3. Decreased energy

Accompanying symptoms:
1. Loss of confidence and self-esteem
2. Self-reproach / inappropriate guilt
3. Thoughts of death or suicide
4. Diminished ability to think/concentrate
5. Agitation or retardation
6. Sleep disturbance of any type
7. Change in appetite

Severe unipolar depression:
- Duration at least 2 weeks
- No underlying organic cause
- No previous episodes of hypomania, mania or mixed symptoms
- 3 core symptoms and minimum 5 accompanying symptoms*

Severe depression with psychotic features (F32.3 & F33.3):
- Meets criteria for severe unipolar depression
- Presence of
  - Delusion
  - Hallucination
  - Stupor
- Mood-congruent / Mood-incongruent
- Does not meet criteria for schizophrenia/schizoaffective disorder

* Note: If important symptoms such as agitation or retardation are marked, the patient may be unwilling or unable to describe many symptoms in detail. An overall grading of severe episode may still be justified in such a case.

(ICD-10 Criteria for research)
"The valid psychiatric syndrome"

Robins & Guze, 1970

1. Clinical presentation
2. Biology
3. Delimitation from other disorders
4. Specific heritability
5. Course and prognosis
6. (Treatment response)

1. **Clinical presentation**
   - ↑ Psychotic symptoms
   - ↑ Psychomotor disturb.
   - ↑ Cognitive problems
   - ↓ Diurnal variation


2. **Biology**
   - ↑ HPA-axis dysregulation
   - ↓ activity of DβH
   - = Corticosteroid-dopamine hypothesis for PD


3. **Specific heritability**
   - ↓ Heritability in depression
   - ↑ heritability in PD
   - • Familial aggregation in PD


4. **Delimitation from other disorders**
   - • Diagnostic criteria
   - • Psychotic symptoms
   - • Quality of the psychosis
   - • Episodic vs. chronic


5. **Course & Prognosis**
   - ↑ Recurrence rate
   - ↑ Psychosocial impairment
   - ↑ Mortality
   - ↑ Risk of suicide


6. **Treatment response**
   - ↓ Placebo
   - ↓ Antidepressants
   - ↓ Psychotherapy
   - ↑ ECT

ECT for psychotic depression – the evidence

• The Consortium for Research in ECT
  - Acute phase ECT
  - Maintenance phase ECT vs. Nortr + Li
  - Results for psychotic depression

• The Columbia (Sackeim) group
  - Acute phase ECT (bilat. vs. unilat.) and concomitant meds (Nortr vs. Ven)
  - Maintenance phase (Nortr+Li vs. Ven+Li)

• The Navarro study on ECT for late life psychotic depression
  - Effect of ECT+Nortr vs. Nortr

• New paper in the American Journal of Psychiatry
  - Bilateral vs. Unilateral ECT – implications for psychotic depression?
Figure 1. Participant flow for acute electroconvulsive therapy (ECT) phase (phase 1) and randomized continuation phase (phase 2). C-ECT indicates continuation ECT; C-Pharm, combination of lithium carbonate plus nortriptyline hydrochloride.
CORE – ECT procedure

• 531 patients with major depressive disorder – 4 centers

• Meds (antidepressants, mood stabilizers) tapered

• Bilateral ECT - Thymatron DGx device

• Methohexital 0.5-1 mg/kg + succinylcholine 0.75-1 mg/kg

• Seizure threshold determined by dose titration

• 3 ECT sessions per week (1.5 times seizure threshold)

• Treatment until remission* or plateau**

* HAM-D24 < 10 at 2 consecutive ratings

** A change of less than 3 HAM-D24 points in either direction over 2 consecutive measurements
Speed of Response and Remission in Major Depressive Disorder With Acute Electroconvulsive Therapy (ECT): A Consortium for Research in ECT (CORE) Report

*Mustafa M. Husein et al*

<table>
<thead>
<tr>
<th>ECT Session #</th>
<th>First Response</th>
<th></th>
<th>Sustained Response (^a)</th>
<th></th>
<th>Remission (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>1</td>
<td>12.6</td>
<td>32</td>
<td>6.3</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>32.0</td>
<td>81</td>
<td>19.0</td>
<td>48</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>53.8</td>
<td>136</td>
<td>34.8</td>
<td>88</td>
<td>4.0</td>
</tr>
<tr>
<td>4</td>
<td>67.2</td>
<td>170</td>
<td>45.9</td>
<td>116</td>
<td>10.3</td>
</tr>
<tr>
<td>5</td>
<td>78.7</td>
<td>199</td>
<td>58.5</td>
<td>148</td>
<td>21.3</td>
</tr>
<tr>
<td>6</td>
<td>83.4</td>
<td>211</td>
<td>64.4</td>
<td>163</td>
<td>33.6</td>
</tr>
<tr>
<td>7</td>
<td>87.4</td>
<td>221</td>
<td>70.0</td>
<td>177</td>
<td>42.3</td>
</tr>
<tr>
<td>8</td>
<td>89.3</td>
<td>226</td>
<td>73.5</td>
<td>186</td>
<td>53.0</td>
</tr>
<tr>
<td>9</td>
<td>92.5</td>
<td>234</td>
<td>75.9</td>
<td>192</td>
<td>60.5</td>
</tr>
<tr>
<td>10</td>
<td>93.3</td>
<td>236</td>
<td>76.3</td>
<td>193</td>
<td>64.8</td>
</tr>
<tr>
<td>≥ 11</td>
<td>94.1</td>
<td>238</td>
<td>79.1</td>
<td>200</td>
<td>74.7</td>
</tr>
</tbody>
</table>

\(^a\)Sustained response is defined as a response (not necessarily a first response) that is sustained through exit; requires that at least 2 consecutive HAM-D scores meet the response criteria.

\(^b\)Dropouts are considered nonremitters.

\(^c\)Of the total sample, 5.9% (N = 15) never achieved a first response, 20.9% (N = 53) never achieved a sustained response, and 25.3% (N = 64) never achieved remission.

50% decrease from baseline HAM-D24 score
Relief of Expressed Suicidal Intent by ECT: A Consortium for Research in ECT Study

Charles H. Kellner et. al

TABLE 2. Number of ECT Sessions Needed to Resolve Expressed Suicidal Intent Rating (rating=0) for all Depressed Patients, Completers, and Dropouts With Rating ≥3 at Baseline

<table>
<thead>
<tr>
<th>Session Number</th>
<th>Patients With 0 Rating (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Study Group (N=131)</td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>101</td>
</tr>
<tr>
<td>&gt;10</td>
<td>106</td>
</tr>
<tr>
<td>No ECT</td>
<td>25</td>
</tr>
</tbody>
</table>
ECT Remission Rates in Psychotic Versus Nonpsychotic Depressed Patients: A Report from CORE

Georgios Petrides et. al

"The outcome of an acute ECT course in 253 patients with nonpsychotic (n=176) and psychotic (n =77) unipolar major depression was assessed in the first phase of an ongoing National Institute of Mental Health supported four-hospital collaborative study.”

“The overall remission rate was 87% for study completers. Among these, patients with psychotic depression had a remission rate of 95% and those with nonpsychotic depression, 83%. Improvement in symptomatology, measured by the HRSD, was more robust and appeared sooner in the psychotic patients compared with the nonpsychotic patients.”
ECT is extremely effective for the acute treatment of major depression, but has not been properly tested for relapse prevention.

Patients having obtained remission in response to acute ECT were randomized to either maintenance ECT or treatment with nortriptyline + lithium carbonate (adjusted to achieve steady-state levels of 125 ng/mL of nortriptyline and 0.7 mEq/L of lithium).

The primary efficacy outcome measure was time to relapse (HAM-D24 total score of 16 or higher, with a minimum increase of 10 points from phase 2 baseline).

ECT group: 37.1% relapse, 16.8% drop-out
Nortr.+Li: 31.6% relapse and 22.1% drop-out

Sackeim et al. JAMA 2001: Relapse rate placebo = 84%

What about those with psychotic depression?
"A patient with psychotic features is 0.56 times less likely to relapse than a patient without psychotic features, after adjustment for treatment, age, sex, and center"

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment†</td>
<td>1.13 (0.69-1.36)</td>
<td>.62</td>
</tr>
<tr>
<td>Treatment‡</td>
<td>1.18 (0.71-1.94)</td>
<td>.53</td>
</tr>
<tr>
<td>Psychosis‡</td>
<td>0.56 (0.32-1.00)</td>
<td>.05</td>
</tr>
<tr>
<td>Age§</td>
<td>0.99 (0.97-1.00)</td>
<td>.13</td>
</tr>
<tr>
<td>Sex¶</td>
<td>0.63 (0.37-1.08)</td>
<td>.09</td>
</tr>
</tbody>
</table>

Relapse rates stratified on psychosis status

<table>
<thead>
<tr>
<th>Status</th>
<th>All</th>
<th>C-ECT</th>
<th>Nortr+Li</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic (n=66)</td>
<td>29%</td>
<td>32%</td>
<td>26%</td>
</tr>
<tr>
<td>Non-psychotic (n=118)</td>
<td>45%</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.009</td>
<td>0.159</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Previously unpublished results. Courtesy of Georgios Petrides, MD (CORE)
Effect of Concomitant Pharmacotherapy on Electroconvulsive Therapy Outcomes

Harold A. Sackeim et. al

- Hypotheses:
  - “Compared with placebo, concomitant treatment with nortriptyline or venlafaxine during the ECT course enhances short-term efficacy without a meaningful effect on adverse effects”.
  - “High-dose, right-sided, unilateral ECT is equivalent in efficacy to moderate-dosage bilateral ECT and retains advantages with respect to cognitive adverse effects”.

- Participants: 319 patients with major depressive episode (unipolar or bipolar). HAM-D24 ≥ 21

- Randomization 1: Participants were randomized to right unilateral (RUL) ECT (6 × seizure threshold) or bilateral (BL) ECT (1.5 × seizure threshold). MECTA Spectrum 5000Q device.

- Randomization 2: Participants were also randomized to receive either placebo, venlafaxine (min. 225 mg), or nortriptyline (blood levels 100-120 ng/mL).

- Treatment duration: Electroconvulsive therapy was continued as long as clinical progress was observed and terminated after no further improvement for at least 2 treatments.

- Remission: At least a 60% reduction in HAM-D24 scores relative to pre-ECT baseline, with a maximum score of 10 at both within 2 days of ECT discontinuation and at a reassessment 4 to 8 days following ECT termination.
Figure 2. Remission rates for the pharmacological (A) and electroconvulsive therapy (ECT) electrode placement (B) conditions as a function of requiring a different number of treatments to be classified as a betterer in the context of lack of remission. More stringent criteria result in an overall increase in remission rates, but have little effect on the differences among the pharmacological and ECT conditions.

Figure 3. Mean post–electroconvulsive therapy (ECT) standard scores (with standard error) for the pharmacological (A) and ECT electrode placement (B) conditions on the 4 primary cognitive outcome measures. Nortriptyline had a significant advantage over venlafaxine on the modified Mini-Mental State Examination (MMSE) and Buschke Selective Reminding Test (SRT) and over placebo on the N-Back d’ measures. Right unilateral ECT had superior cognitive outcomes compared with bilateral ECT on the Buschke SRT and the Columbia University Autobiographical Memory Interview, Short Form (AMI-SF).
Pharmacological Strategies in the Prevention of Relapse After Electroconvulsive Therapy

Joan Prudic et. al

“Objective: To determine whether starting antidepressant medication at the start of electroconvulsive therapy (ECT) reduces post-ECT relapse and to determine whether continuation pharmacotherapy with nortriptyline (NT) and lithium (Li) differs in efficacy or adverse effects from continuation pharmacotherapy with venlafaxine (VEN) and Li.”

“Methods: During an acute ECT phase, 319 patients were randomized to treatment with moderate dosage bilateral ECT or high-dosage right unilateral ECT. They were also randomized to concurrent treatment with placebo, NT, or VEN. Of 181 patients to meet post-ECT remission criteria, 122 (67.4%) participated in a second continuation pharmacotherapy phase. Patients earlier randomized to NT or VEN continued on the antidepressant, whereas patients earlier randomized to placebo were now randomized to NT or VEN. Lithium was added for all patients who were followed until relapse or 6 months.”

Relapse = HAM-D24 score of at least 16 maintained for at least one week and a mean absolute increase of at least 10 HAM-D24 points compared to continuation phase baseline.

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>$\chi^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>2</td>
<td>9.76</td>
<td>0.0077</td>
</tr>
<tr>
<td>HRSD at continuation trial baseline</td>
<td>1</td>
<td>3.38</td>
<td>0.07</td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>11.56</td>
<td>0.0007</td>
</tr>
<tr>
<td>Total no. antidepressant trials, current episode</td>
<td>1</td>
<td>5.52</td>
<td>0.02</td>
</tr>
<tr>
<td>Psychosis, yes/no</td>
<td>1</td>
<td>0.11</td>
<td>0.74</td>
</tr>
<tr>
<td>Unipolar vs bipolar</td>
<td>1</td>
<td>2.47</td>
<td>0.12</td>
</tr>
<tr>
<td>HRSD at pre-ECT study entry</td>
<td>1</td>
<td>0.02</td>
<td>0.88</td>
</tr>
<tr>
<td>ECT assignment (BL vs RUL)</td>
<td>1</td>
<td>0.01</td>
<td>0.91</td>
</tr>
<tr>
<td>Total no. ECTs</td>
<td>1</td>
<td>1.29</td>
<td>0.26</td>
</tr>
</tbody>
</table>

TABLE 3. Parametric Survival Analysis on Relapse-Time Data

TABLE 4. Parametric Survival Analysis of Clinical Predictors of Relapse-Time Data
Pharmacological Strategies in the Prevention of Relapse After Electroconvulsive Therapy

Joan Prudic et. al

**FIGURE 1.** Kaplan-Meier estimates of the proportion of patients who remained well during the continuation pharmacotherapy trial for patients randomized to treatment with PL or antidepressant medication (NT or VEN) during the ECT course.

**FIGURE 2.** Kaplan-Meier estimates of the proportion of patients who remained well during the continuation trial for patients randomized to treatment with NT-Li or VEN-Li as continuation pharmacotherapy.
Continuation/Maintenance Treatment with Nortriptyline Versus Combined Nortriptyline and ECT in Late-Life Psychotic Depression: A Two-Year Randomized Study

Victor Navarro et al.

- > 60 years meeting DSM-IV criteria for unipolar psychotic depression (HAM-D17 > 21 or greater)
- Phase 1: Bilateral ECT* 3 times per week + Nortriptyline adjusted to blood level between 80-120 ng/mL (max dose 100 mg/day). Treatment until remission (HAM-D17 score <8 at 3 ratings).
- Phase 2: Phase 1 remitters were randomized to either maintenance ECT**+Nortriptyline or Nortriptyline monotherapy***. Assessed at weeks 0, 2, and 4, and then monthly.
- Relapse/recurrence: meeting symptomatic criteria for DSM–IV major depression and having a HAM-D17 score of 16 or above at 2 consecutive ratings.

* MECTA-SR2 ECT device. Seizure threshold was titrated at treatment 1. Succinylcholine (40–100 mg), atropine (0.5– 1 mg), and thiopental (200–300 mg) were used for anesthesia.

** Weekly treatment for the first month, every 2 weeks for the following month, and then monthly.

*** This group received up to 2 mg risperidone for 6 weeks – which was then tapered over 4 weeks.
38 Entered acute ECT phase

1 Without disease remission
33 With disease remission
4 Premature exits (3 adverse event, 1 protocol violation)

33 Randomized into follow-up phase

17 Monotherapy (Nortriptyline)
16 Combined treatment (Nortriptyline+ECT)

4 Premature exits (1 died, 1 loss of follow-up, 1 adverse event, 1 protocol violation)

13 Completers
12 Completers
4 Premature exits (1 breast cancer, 1 adverse event, 2 protocol violations)

8 With disease relapse (2) or recurrence (6)
5 Without relapse or recurrence
11 Without relapse or recurrence
1 With disease relapse (1) or recurrence (0)
Bitemporal Versus High-Dose Unilateral Twice-Weekly Electroconvulsive Therapy for Depression (EFFECT-Dep): A Pragmatic, Randomized, Non-Inferiority Trial


Objective: ECT is the most effective treatment for severe depression. Previous efficacy studies, using thrice-weekly brief-pulse ECT, reported that high-dose (6× seizure threshold) right unilateral ECT is similar to bitemporal ECT but may have fewer cognitive side effects. The authors aimed to assess the effectiveness and cognitive side effects of twice-weekly moderate-dose (1.5× seizure threshold) bitemporal ECT with high-dose unilateral ECT in real-world practice.

Method: This was a pragmatic, patient- and rater-blinded, noninferiority trial of patients with major depression (N=138; 63% female; age=56.7 years [SD=14.8]) in a national ECT service with a 6-month follow-up. Participants were independently randomly assigned to bitemporal or high-dose unilateral ECT. The primary outcome was change in the 24-item Hamilton Depression Rating Scale (HAM-D) score after the ECT course; the prespecified noninferiority margin was 4.0 points. Secondary outcomes included response and remission rates, relapse status after 6 months, and cognition.

Results: Of the eligible patients, 69 were assigned to bitemporal ECT and 69 to unilateral ECT. High-dose unilateral ECT was noninferior to bitemporal ECT regarding the 24-item HAM-D scores after the ECT course (mean difference=1.08 points in favor of unilateral ECT [95% CI=−1.67 to 3.84]). There were no significant differences for response and remission or 6-month relapse status. Recovery of orientation was quicker following unilateral ECT (median=19.1 minutes versus 26.4 minutes). Bitemporal ECT was associated with a lower percent recall of autobiographical information (odds ratio=0.66) that persisted for 6 months.

Conclusions: Twice-weekly high-dose unilateral ECT is not inferior to bitemporal ECT for depression and may be preferable because of its better cognitive side-effect profile.

“Our findings show that twice-weekly high-dose unilateral ECT is noninferior to bitemporal ECT for severe depression in regular clinical practice, which included continued antidepressant pharmacotherapy, and this was maintained over 6 months.”

Psychotic depression (bipolar/unipolar) = 21% of sample. RUL is effective for those as well.

(personal correspondance – Declan M. McLoughlin)
(Tentative) conclusions for psychotic depression based on current ECT evidence

- CORE/Kellner/Petrides: BIL ECT is very effective in the acute phase of psychotic depression.
- Petrides: For relapse prevention, Nort + Li appears to be (at least) equally effective as BIL ECT.
- Petrides: Neither Nort. + Li nor BIL ECT are ideal for relapse prevention (~30% relapses in 6 months).
- Navarro: Relapse prevention using BIL ECT + Nort has shown promise in late life psychotic depression.
- Sackeim: Acute ECT+Nortr is better than ECT+Placebo (not stratified uni/bi or psych/non).
- Sackeim: Acute RUL is equally effective as BIL with less side effects (not stratified uni/bi or psych/non).
- Prudic: Starting an AD in acute ECT phase = no effect on relapse (not stratified uni/bi or psych/non).
- Prudic: Old age is a predictor for sustained remission (not stratified uni/bi or psych/non).
- Semkovska: RUL is equally effective as BIL with less side effects (not stratified uni/bi or psych/non).
- McLoughling: True for psychotic depression (not stratified uni/bi) as well.
A potential future studies on ECT for psychotic depression
- Knowing what we know now -

"PILOT STUDY":

- Patients with psychotic depression aged ≥50.

- Double-blind randomized study:
  1. High-dose RUL ECT (3 weekly) + nortriptylin
  2. BIL ECT (3 weekly) + nortriptylin

- Acute phase: Treatment until remission* or plateau.

- Maintenance phase: Those having obtained remission in the acute phase will remain in the treatment group assigned for the acute phase. ECT schedule: Weekly treatment for the first month, every 2 weeks for the second month, and then monthly for 4 months

* Defined by the Psychotic Depression Assessment Scale (PDAS) = a total score <8 at two consecutive ratings