ECT in bipolar disorder depression. Results from the Norwegian RCT

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Long-term symptomatic status

Percentage of total follow-up weeks

Bipolar disorder type I
- Asymptomatic
- Depression
- (Hypo)Mania
- Cycling/mixed episode

Bipolar disorder type II
- Asymptomatic
- Depression
- (Hypo)Mania
- Cycling/mixed episode

Judd et al., 2002 and 2003
Acute treatment of bipolar depression

- Psychosocial treatment: psychoeducation, cognitive behavioral therapy, interpersonal and social rhythm therapy (IPSRT), family-focused therapy
- Pharmacological treatment:
  - anticonvulsant mood stabilizers
  - atypical antipsychotics
  - Lithium
  - antidepressants (in combination with mood stabilizer)
- Electroconvulsive therapy (ECT)
Guidelines and treatment algorithms

- differing recommendations
- paucity of research and differences in interpreting the evidence
- most controversial: use of antidepressants in bipolar depression
- place of ECT differs between the algorithms
  - Psychopharmacology algorithm project at the Harvard South Shore Program: **first** assess whether there is an urgent indication for ECT
# Studies on ECT in UP and BP depressed patients

<table>
<thead>
<tr>
<th>Study</th>
<th>UP</th>
<th>BP</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black et al., 1987</td>
<td>70%</td>
<td>69%</td>
<td>markedly improved</td>
</tr>
<tr>
<td>Daly et al., 2001</td>
<td>42%</td>
<td>48%</td>
<td>remission rate</td>
</tr>
<tr>
<td>Grunhaus et al., 2002</td>
<td>36%</td>
<td>30%</td>
<td>remission rate</td>
</tr>
<tr>
<td>Kho et al., 2005</td>
<td>66%</td>
<td>73%</td>
<td>remission rate</td>
</tr>
<tr>
<td>Bailine et al., 2009</td>
<td>61%</td>
<td>64%</td>
<td>remission rate</td>
</tr>
<tr>
<td>Sienaert et al., 2009</td>
<td>65%</td>
<td>69%</td>
<td>remission rate</td>
</tr>
<tr>
<td>Homan et al., 1982</td>
<td>43%</td>
<td>23%</td>
<td>markedly improved</td>
</tr>
</tbody>
</table>
Response to ECT in bipolar I, bipolar II and unipolar depression

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n=130 (17 UP 67 BP II 46 BP I)

Response rate: 94 % 79 % 67 %
Remission rate: 70 % 57 % 65 %

UP: best results
BP I: residual manic and psychotic symptoms
ECT in bipolar depression

- Clinical experience and some older studies \cite{Bratfos og Haug, 1965}
- Minor role in treatment guidelines
- No RCT
- Inconsistency in the literature regarding cognitive side effects
Cognition in Bipolar Disorder

Lewandowski, 2011
Aims of the study

- neurocognitive functioning in treatment-resistant, acutely admitted bipolar depression patients
- efficacy of ECT compared to algorithm-based pharmacological treatment (APT)
- effects of ECT and APT on general neurocognitive function and autobiographical memory shortly after treatment
Background
- No randomized controlled trials of ECT in bipolar depression

Design (1:1 randomization)
- A prospective, randomized controlled, multi-centre six-week acute treatment trial (9 sites)
- Follow up visit at 26 weeks or until remission (max 52 weeks)
- Intervention group
  - 3 sessions per week for up to 6 weeks, total up to 18 sessions
- Control group
  - algorithm-based pharmacological treatment as usual

Neuropsychological tests before, during and after ECT

Genetic and biochemical studies (cytokines)
The Norwegian randomized controlled trial of electroconvulsive therapy in treatment resistant bipolar depression

73 patients randomized 1:1

Bipolar disorder 1 or 2
MADRS > 25
Treatment resistant

Exclusion criteria:
Former non-response to ECT, ECT during last 6 months, rapid cycling bipolar disorder, unstable medical conditions, neurological disorders
BRAIN
Bipolar Research And Innovation Network

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Treatment in control group

Algorithm based pharmacological treatment – APT

Adapted from Goodwin and Jamison, 2007

Step 1
If not on a mood stabilizer
- Start lamotrigine combined with lithium or valproate
- For severe depression:
  consider an AD plus an antimanic mood stabilizer
- For psychotic depression:
  add an atypical antipsychotic

If on lithium or valproate
- If on lithium, increase dose
- Add lamotrigine

Step 2
Add quetiapine

Step 3
Consider OFC as an alternative to quetiapine

Step 4
Discontinue OFC and add an AD, while maximizing the dosage of the antimanic mood stabilizer.
ECT procedures

• 3 treatments per week up to 6 weeks
• Thiopental in lowest possible dosage (1.5-2.5 mg/kg iv)
• Succinylcholine (0.5 – 1.0 mg/kg iv)
• Hyperoxygenation /hyperventilation
• RUL
• Charge: 0.5 ms pulse width, age based dose, adjusted at subsequent treatments
  based on clinical effect, seizure duration, quality of δ-waves, seizure ending, postictal suppression, postictal reorientation time
Assessment

Pre

Washout

Time, weeks

1 2 3 4 5 6

Treatment

MADRS, IDS, YMRS, CGI-BP

Neurocognitive assessment

Illness characteristics
<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of processing</td>
<td>Brief Assessment of Cognition in Schizophrenia: Symbol-Coding Category Fluency: Animal Naming Trail Making Test: Part A</td>
</tr>
<tr>
<td>Attention/ vigilance</td>
<td>Continuous Performance Test—Identical Pairs (CPT-IP)</td>
</tr>
<tr>
<td>Working memory</td>
<td>Wechsler Memory Scale® (WMS®-III): Spatial Span Letter-Number Span</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>Hopkins Verbal Learning Test—Revised™ (HVLT-R™)</td>
</tr>
<tr>
<td>Visual learning</td>
<td>Brief Visuospatial Memory Test—Revised (BVMT-R™)</td>
</tr>
<tr>
<td>Reasoning/ problem solving</td>
<td>Neuropsychological Assessment Battery® (NAB®): Mazes</td>
</tr>
</tbody>
</table>

(Social cognition)
Flow chart

Randomized
\( n=73 \)

- ECT
  \( n=38 \)
  Did not receive allocated intervention, \( n=2 \)
  Analyzed as ITT
  \( n=36 \)
  Drop out
  \( n=13 \)
  Completed ECT
  \( n=23 \)

- APT
  \( n=35 \)
  - Did not receive allocated intervention, \( n=2 \)
  - No post-baseline assessment, \( n=3 \)
  Analyzed as ITT
  \( n=30 \)
  Drop out
  \( n=10 \)
  Completed APT
  \( n=20 \)

Remission and response rate

Not eligible for neurocognitive assessment
\( n=22 \)

Baseline neuropsychological assessment
\( n=51 \)

Did not complete randomized treatment or testing after treatment
\( (n_{ECT}=9, n_{APT}=3) \)

Neurocognitive assessment after randomized treatment
\( (n_{ECT}=19, n_{APT}=20) \)
## Patient characteristics at inclusion

<table>
<thead>
<tr>
<th></th>
<th>ECT (n=38)</th>
<th>APT (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>21</td>
<td>55.3</td>
</tr>
<tr>
<td>Bipolar disorder type I</td>
<td>14</td>
<td>36.8</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age at inclusion</td>
<td>48.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Illness duration (years)</td>
<td>31.8</td>
<td>12.2</td>
</tr>
<tr>
<td>Number of depressive episodes</td>
<td>22.3</td>
<td>24.2</td>
</tr>
<tr>
<td>Number of manic episodes</td>
<td>2.7</td>
<td>8.6</td>
</tr>
<tr>
<td>MADRS</td>
<td>39.1</td>
<td>7.5</td>
</tr>
<tr>
<td>CGI-BD</td>
<td>5.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Speed of Processing
Attention/Vigilance
Working Memory
Verbal learning
Visual learning
Reasoning

T-score

Normal Mean

Clinical Impairment

Bipolar II
Bipolar I

T-score
30
35
40
45
50
55
Neurocognitive profiles in treatment-resistant bipolar I and bipolar II disorder depression

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Abstract

Background: The literature on the neuropsychological profiles in Bipolar disorder (BD) depression is sparse. The aims of the study were to assess the neurocognitive profiles in treatment-resistant, acutely admitted BD depression inpatients, to compare the neurocognitive functioning in patients with BD I and II, and to identify the demographic and clinical illness characteristics associated with cognitive functioning.

Methods: Acutely admitted BD I (n = 19) and BD II (n = 32) inpatients who fulfilled the DSM-IV-TR criteria for a major depressive episode were tested with the MATRICS Consensus Cognitive Battery (MCCB), the Wechsler Abbreviated Scale of Intelligence, the National Adult Reading Test, and a battery of clinical measures.

Results: Neurocognitive impairments were evident in the BD I and BD II depression inpatients within all MCCB domains. The numerical scores on all MCCB-meaures were lower in the BD I group than in the BD II group, with a significant difference on one of the measures, category fluency. 68.4% of the BD I patients had clinically significant impairment (>1.5 SD below normal mean) in two or more domains compared to 37.5% of the BD II patients (p = 0.045). A significant reduction in IQ from the premorbid to the current level was seen in BD I but not BD II
Change in MADRS score

- **APT (Algorithm based pharmacological treatment)**
  - IME-analysis
  - $p = 0.001$
  - 6.6 points

- **ECT**

Graph showing the change in MADRS score over time (days) with a downward trend for both APT and ECT treatments.
Response and remission rate

ECT

APT

Response

Remission
New Research

Treatment-Resistant Bipolar Depression: A Randomized Controlled Trial of Electroconvulsive Therapy Versus Algorithm-Based Pharmacological Treatment

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Change (improvement) of performance on cognitive tasks (MATRICS) from pre- to post-treatment
Autobiographical memory

- Memory of personal events and facts
- essential for:
  - self-definition
  - social interaction
  - and as a guide for present and future activities and problem-solving
- methodological challenges associated with assessment
Autobiographical Memory

\[ p = 0.025 \]

\[ \text{ECT} \]
\[ \text{APT} \]

72.9

80.8
The Effect of Electroconvulsive Therapy on Neurocognitive Function in Treatment-Resistant Bipolar Disorder Depression

Ute Kessler, MD; Helle K. Schoeyen, MD, PhD; Ole A. Andreassen, MD, PhD; Geir E. Eide, PhD; Ulrik F. Malt, MD, PhD; Ketil J. Oedegaard, MD, PhD; Gunnar Morken, MD, PhD; Kjetil Sundet, PhD; and Arne E. Vaaler, MD, PhD

ABSTRACT
Objective: To compare the effects of right unilateral (RUL) electroconvulsive therapy (ECT) and algorithm-based pharmacologic treatment (APT) on neurocognitive function in treatment-resistant bipolar disorder depression.

Method: Inpatients with DSM-IVTR-diagnosed, treatment-resistant bipolar depression, who were acutely admitted to 1 of the 7 clinical study centers in Norway, were recruited from May 2008 to April 2011 into a prospective, randomized controlled, 6-week acute treatment trial. General neurocognitive function was assessed with the MATRICS Consensus Cognitive Battery (MCCB), and retrograde memory for autobiographical events was assessed with the Autobiographical Memory Interview–Short Form (AMI-SF) before and shortly after (mean = 23.5 days) a trial with either RUL brief-pulse ECT (mean dose = 233.3 mC) or APT.

Results: Seventy-three patients entered, and 39 (nECT = 19, nAPT = 20) completed. Both groups showed improvements in all MCCB domain scores, with no significant differences between groups on any measure. No participant reported significant memory problems after ECT.

Bipolar disorder is associated with modest neurocognitive impairments in all phases of the illness, across all neuropsychological domains, and with a moderate worsening of a subset of deficits in the acute states.1-3 Pharmacologic treatments exert various effects on cognitive function in bipolar disorder. Psychoactive drugs may improve cognition by targeting psychotic and mood symptoms or worsen it due to side effects mediated by anticholinergic, sedative, extrapyramidal, and blunting mechanisms.4 However, the present evidence is limited since no large and fully powered randomized controlled trials have been performed.4 Electroconvulsive therapy (ECT) is widely regarded as an effective treatment in bipolar depression, is shown to be equally effective in unipolar and bipolar depression,5 and has some documentation in the treatment of treatment-resistant patients.6 However, the clinical use of ECT is accompanied by safety concerns due to the potentially unfavorable long-lasting effects on memory and other neurocognitive functions.7,8

The literature on the severity, persistency, and pattern of neurocognitive deficits induced by ECT is inconsistent.9 This is mainly due to methodological factors related to distinguishing
Limitations

- Small sample, high drop out rate
- No data on long-term outcomes
- RUL?
- Exclusion of severely ill patients
Summary

ECT more effective in reducing depressive symptoms than algorithm based pharmacological treatment

General neurocognitive function unaffected by ECT

Reduced autobiographical memory after ECT
Collaborators

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