ECT in Schizophrenia

Dr Richard Braithwaite
Consultant Psychiatrist
Isle of Wight NHS Trust
ECT in Schizophrenia
(not catatonia)

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Consultant Psychiatrist
Isle of Wight NHS Trust
Objectives

• History
• Current guidance
• Current usage
• Evidence base
  – overall
  – TRS (clozapine)
• Conclusions
• Recommendations
History

- ECT devised as a treatment for schizophrenia
- Trials from 1940s onwards mainly focused on depressive illness
- 1954 – chlorpromazine
- Subsequent antipsychotics
- Pharmaceutical marketing
- Stigma against ECT from 1960s onwards
Current guidance
NICE TA59 (2003)

• The current state of the evidence does not allow the *general* use of ECT in the management of schizophrenia to be recommended.

*(my italics)*
“The treatment of choice for acute schizophrenia is antipsychotic drug treatment. ECT may be considered as an option for treatment-resistant schizophrenia, where treatment with clozapine has already proven ineffective or intolerable. There is presently no evidence to support the use of ECT as a maintenance treatment in schizophrenia.”

Fear, Dunne & McLoughlin
Current usage
Leiknes et al (2012)

- systematic review of studies of ECT usage
- 1990 – 2011
- included indications for ECT

Leiknes et al. *Brain & Behavior* 2012; 2: 283-302
British Isles

- ECTAS data
  - excludes Scotland
  - 71 / 117 (61%) clinics in E, W, NI &RoI
## ECTAS minimum dataset 2016-17

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No of people</th>
<th>% of people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catatonia</td>
<td>54</td>
<td>3.0</td>
</tr>
<tr>
<td>Moderate depression that has not responded to drug treatments and psychological treatment</td>
<td>779</td>
<td>42.8</td>
</tr>
<tr>
<td>Severe depression that is life-threatening, and where a rapid response is required, or where other treatments have failed</td>
<td>826</td>
<td>45.4</td>
</tr>
<tr>
<td>Prolonged or severe manic episode</td>
<td>60</td>
<td>3.3</td>
</tr>
<tr>
<td>Other</td>
<td>102</td>
<td>5.6</td>
</tr>
</tbody>
</table>
ECTAS minimum dataset 2016-17

breakdown of “other”:

<table>
<thead>
<tr>
<th>Reason for referral</th>
<th>No of people</th>
<th>% of people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusional disorder</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>13</td>
<td>0.7</td>
</tr>
<tr>
<td>Psychosis</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>Patient request</td>
<td>8</td>
<td>0.4</td>
</tr>
<tr>
<td>Deteriorating mental state</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Not responsive to other treatments</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>Diagnosis uncertain</td>
<td>1</td>
<td>0.05</td>
</tr>
</tbody>
</table>
ECTAS minimum datasets

patients with schizophrenia
ECTAS minimum dataset 2016-17

patients with schizophrenia

- Male
- Female

- Male
- Female
ECTAS minimum dataset 2016-17

- Schizophrenia:
  - Mean age

- All patients:
  - Mean age
ECTAS minimum dataset 2016-17

patients with schizophrenia

- Detained, incapacitated
- Informal, capacitous

[Pie chart showing the distribution of patients with schizophrenia]
ECTAS minimum dataset 2016-17

patients with schizophrenia

The bar chart shows the number of patients with schizophrenia in the ECTAS minimum dataset 2016-17, categorized by improvement levels:

- No change: 2 patients
- Minimally improved: 5 patients
- Much improved: 5 patients
- Very much improved: 1 patient
Evidence base
Cochrane Review (2005)

- Tharyan & Adams
- 26 RCTs
- Variable quality
- 5 decades of research
- Various different outcomes and comparisons
- Generally unable to separate acute patients from chronic or treatment-resistant patients
Summary of Cochrane Review

• ECT better than sham ECT in the short-term
  NNT=6 (CI 4-12)
• ECT less effective than antipsychotics in the short-term
• Limited evidence that addition of ECT to antipsychotics produces a faster and greater response in the short-term
• cECT + antipsychotic reduces risk of relapse compared to antipsychotics alone in medication-resistant patients
  NNT=2 (95% CI 1.5-2.5)
• No difference in efficacy between UL and BL
• 20 treatments may be superior to 12

Systematic Review in 2013 (Pompili et al) revealed no new RCTs since
Treatment-Resistant Schizophrenia

- failure of two antipsychotics
- 30% patients with schizophrenia

• systematic review and meta-analysis
• TRS
• RCTs comparing:
  – ECT augmentation of non-clozapine antipsychotic
  – the same antipsychotic alone +/- sham ECT
• n=11 RCTs
• China 9, Thailand 1, India 1
• n=818 patients
• Study-defined response
  – ECT + AP → 51%
  – AP → 33%
  – NNT 6 (95%CI 3.9-9.4)
• Study-defined remission
  – ECT + AP → 21%
  – AP → 9%
  – NNT 9 (5.8-17.1)
• Memory impairment NNH 3 (2-5)
• Headache NNH 6 (4-11)
Which treatment-resistant patients will respond to ECT?
Chanpattana & Sackeim (2010)

• n=253
• prospectively treated with:
  – BL ECT x3/wk, ST titration, up to 20 treatments (fewer if earlier response) AND
  – flupentixol p.o. 24mg/day
• response = BPRS < 25
• 55% response rate
• responders had a mean of 12.5 ECTs (SD 4.3)
<table>
<thead>
<tr>
<th></th>
<th>All (n=253)</th>
<th>Male (n=117)</th>
<th>Female (n=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\chi^2$</td>
<td>$p$</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td>Age, yr</td>
<td>0.06</td>
<td>0.86</td>
<td>0.56</td>
</tr>
<tr>
<td>Duration of illness, yr</td>
<td>1.28</td>
<td>0.26</td>
<td>0.55</td>
</tr>
<tr>
<td>Duration of episode, yr</td>
<td>20.49</td>
<td>&lt;0.0001</td>
<td>10.26</td>
</tr>
<tr>
<td>Psychiatric admissions, n</td>
<td>6.23</td>
<td>0.01</td>
<td>5.87</td>
</tr>
<tr>
<td>Paranoid subtype</td>
<td>5.79</td>
<td>0.02</td>
<td>5.36</td>
</tr>
<tr>
<td>FH$_x$ of schizophrenia</td>
<td>4.03</td>
<td>0.045</td>
<td>0.44</td>
</tr>
<tr>
<td>GAF score</td>
<td>4.44</td>
<td>0.04</td>
<td>0.58</td>
</tr>
<tr>
<td>MMSE score</td>
<td>6.45</td>
<td>0.01</td>
<td>1.24</td>
</tr>
</tbody>
</table>

Logistic regression analysis - prediction of response

Chanpattana W & Sackeim HA. *J ECT* 2010; **26**: 289-298.
<table>
<thead>
<tr>
<th>BPRS subscale score</th>
<th>Responders (n=138)</th>
<th>Non-responders (n=115)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thought disturbance</td>
<td>12.2 (2.8)</td>
<td>12.9 (3.5)</td>
<td>-1.75</td>
<td>0.08</td>
</tr>
<tr>
<td>Anxiety-depression</td>
<td>4.6 (3.9)</td>
<td>3.0 (3.2)</td>
<td>3.46</td>
<td>0.0008</td>
</tr>
<tr>
<td>Withdrawal-retardation</td>
<td>8.1 (4.1)</td>
<td>10.5 (4.2)</td>
<td>-4.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Activation</td>
<td>11.2 (3.0)</td>
<td>11.3 (2.8)</td>
<td>-0.30</td>
<td>0.76</td>
</tr>
<tr>
<td>Hostility-suspiciousness</td>
<td>10.1 (4.0)</td>
<td>10.1 (3.6)</td>
<td>0.14</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Values are mean (SD). $t_{251}$ values compare responders & non-responders in baseline BPRS.

Chanpattana W & Sackeim HA. *J ECT* 2010; **26**: 289-298.
Chanpattana & Sackeim (2010)
Predictors of response to ECT in TRS:

- Shorter duration of episode
- Less severe negative symptoms
Clozapine

• indicated after failure of two antipsychotics
• =30% patients with schizophrenia
• clozapine underused
• clozapine failure in 30% to 70%
• meta-analyses show little advantage of pharmacological augmentation in clozapine failure
Masoudzadeh & Khalilian (2007)

• clozapine-naïve TRS
• n=18, Iran
• 3 groups:
  – ECT + Placebo
  – Clozapine + Sham ECT
  – ECT + Clozapine
• randomised
• double blind
• ECT:
  – unilateral
  – dosing unspecified
  – x 3 per week for 4 weeks
  – 12 treatments

• clozapine-resistant TRS
• n=39, New York state
• 2 groups:
  – ECT + Clozapine
  – Clozapine (non-responders then given ECT)
• randomised
• single blind
• ECT:
  – bilateral
  – 1.5 x ST
  – x 3 per week for 4 weeks, then
    x 2 per week for 4 weeks
  – max 20 treatments (mean 15)
  – (if plateau in improvement reached and response criterion met, frequency reduced to weekly until the end of 8 weeks)
Response = 40% ↓ on BPRS psychotic $S_x$ subscale

$z = 4.279 \ p < 0.0001$  

NNT $2.053 \ (95\% CI 1.405 – 3.811)$

Lally et al (2016)

• systematic review and meta-analysis
• augmentation of clozapine with ECT in TRS
• n=5 trials (1 RCT, 4 open)
• n=71 patients
• overall response rate 54% (CI 21.8% – 83.6%)
Lally et al (2016)

- n=29 trials (2 RCT, 4 open, 2 retrospective chart reviews, 6 case series, 15 case studies)
- n=192 patients
- mean ECTs to augment clozapine – 11.3
- 62 patients had f/u data (range 3-468 weeks)
  - 32% relapsed following cessation of ECT
- 5 out of 192 had a prolonged seizure
- minimal cognitive side effects (reporting bias)
Lally et al (2016)

• Conclusions:
  – ECT may be a safe and effective clozapine augmentation strategy in TRS
  – Higher number of ECTs may be required than is standard for other clinical indications
  – Further research needed!

• clozapine-resistant TRS
• n=23, São Paulo
• 2 groups:
  – ECT + Clozapine
  – Sham ECT + Clozapine
• randomised
• single (rater) blind or double blind? Unclear
• ECT:
  – bilateral
  – “standard ST titration and dosing”
  – x 3 per week for 4 weeks
  – total 12 treatments
Response = 40% ↓ on PANSS +ve Sx subscale

z=1.000 p=0.3174

Electrode placement

- meta-analysis BL vs UL – no difference
- only one double-blind RCT → BF vs BT ECT
- n=81 non-catatonic patients
- mean illness duration – 5 years
- mean episode duration – 20 months
- range 4 to 16 treatments; mean 8
NNT=3
(95%CI=1.5-3.2)

NNT=7
(95%CI=3.2-50.2)

Response = 40% ↓ on total BPRS

Conclusions

• ECT was invented to treat schizophrenia
• ECT is very rarely used for schizophrenia in the UK
• ECT is very widely used for schizophrenia elsewhere
• ECT is effective, at least in the short term
• Antipsychotics are more effective than ECT for most patients
• ECT augmentation of non-clozapine antipsychotics in TRS is effective, with positive outcomes associated with shorter episode duration and fewer negative symptoms

• ECT augmentation of clozapine in super-resistant illness may be effective
• Patients may need more treatments than for affective disorder

• The evidence base rests largely on thrice weekly treatments

• UL and BL placements do not differ in efficacy; BF appears superior to BT

• cECT / mECT may be beneficial for patients who have responded to an acute course
Recommendations

• ECT augmentation should be considered **early in TRS and immediately in all cases of clozapine failure**
• 10 to 12 treatments should be given before concluding ECT has been unsuccessful
• Continue past **16 ECT** if there is gradual improvement
• **Bifrontal ECT** should be considered as a first-line mode of treatment
• **Thrice weekly treatment** should be offered where this is available, but non-availability of thrice-weekly treatment should not preclude treatment

• **cECT / mECT** should be considered following a successful acute course of ECT, especially if antipsychotic medication alone has previously been ineffective in preventing relapse / recurrence, or cannot be tolerated