Repetitive Transcranial Magnetic Stimulation (rTMS) and intravenous ketamine for treatment-resistant depression (TRD)

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Disclosures

- No possessions in medical companies
Treatment-resistant depression (TRD)

- Many definitions
- Most common definition: failure to achieve response (50% reduction in symptom severity) in trials with two antidepressants of different classes with adequate doses and sufficient period (Keitner and Mansfield 2012)
- TRD can be classified by different methods (Ruhé et al. 2012)
- Most used classification is Maudsley Staging Model (MSM, Fekadu et al. 2009)
Table 1  Summary of scoring system and domain components of the Maudsley Staging Method

<table>
<thead>
<tr>
<th>Domains</th>
<th>Score range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>1–5</td>
</tr>
<tr>
<td>Failure of augmentations</td>
<td>0–1</td>
</tr>
<tr>
<td>Failure of electroconvulsive therapy</td>
<td>0–1</td>
</tr>
<tr>
<td>Chronicity</td>
<td>1–3</td>
</tr>
<tr>
<td>Severity</td>
<td>1–5</td>
</tr>
<tr>
<td>Total score</td>
<td>3–15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity categories</th>
<th>Score range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>3–6</td>
</tr>
<tr>
<td>Moderate</td>
<td>7–10</td>
</tr>
<tr>
<td>Severe</td>
<td>11–15</td>
</tr>
</tbody>
</table>
Prevalence and outcome of TRD

- Failure to achieve response in 20 – 30 % of patients with major depression (Keitner and Mansfield 2012)
- Only 40 % of patients achieve remission
- 12-month prevalence in Finland about 1 % (Taiminen 2013)
- In a tertiary centre (N = 118, mean MSM 10) 60 % achieved remission during the 8 – 84 months follow-up (Fekadu et al. 2012)
Sickness pensions in Finnish Private Companies in 1983–2009

Depression
F32, F33

Schizophrenia
F20, F23, F25

Anxiety Disorders
F34, F40-42, F44, F45, F48

Alcohol dependence
F10

Personality Disorders
F21, F60–62
Costs of depression in Sweden (Sobocki et al. 2007)
Effect size: examples of Cohen’s d

- 0.2 = height difference (hd) between 15- and 16-year-old girls in population
- 0.5 = hd between 14- and 18-year-old girls
- 0.8 = hd between 13- and 18-year-old girls
- 1 = effect size of placebo response in depression studies
- 1.7 = hd between women and men
Cohen’s d of depression treatments

- < 0.3 Second generation antipsychotic as an adjuvant
- 0.3 – 0.4 Antidepressant or tDCS
- 0.4 – 0.6 Lithium or thyroxin as adjuvants
- 0.6 – 0.7 rTMS
- 0.3 – 0.4 Cognitive psychotherapy
- 0.7 Antidepressant and psychotherapy combined
- 0.9 bilateral or high-energy unilat. ECT
- 1.2 – 1.4 ketamine i.v.
Responder curve of rTMS in depression is biphasic (Downar et al. 2014)
rTMS in depression – early (and primitive) theory

- In depression right DLPFC is hyperactive and left hypoactive
- Right hyperactivity is associated with depression severity and anxiety
- Left hypoactivity is associated with negative emotions
- rTMS aims at restoring balance
Some observations on rTMS in depression

- rTMS releases endogenic opioids (Lamusuo et al. 2017) and dopamine (Cho and Strafella 2009)
- rTMS increases white matter integrity in frontal middle gyrus (Peng et al. 2012) → enhancement of neuroplasticity
- rTMS normalizes brain energy consumption (Li et al. 2010)
- rTMS normalized hyperacticity of temporal areas associated with default mode network (“network of introspection”, Richieri et al. 2017, Ge et al. 2017)
rTMS activates the endogenous opioid system in a wide network (Lamusuo et al. 2017)

Figure 3 Statistical parametric mapping (SPM) analysis shows lower $[^{11}\text{C}]$carfentanil $BP_{ND}$ after active rTMS treatment, compared with sham treatment, in multiple brain regions involved in pain processing ipsilateral and contralateral to rTMS treatment. The ipsilateral cluster comprised of 4477 voxels and had a maximum t value of 5.1 at [4, 48, 36] and a cluster-level corrected $P$-value of <0.001. The contralateral cluster comprised of 2101 voxels and had a maximum t value of 5.7 at [−54, 0, −14] and a cluster-level corrected $P$-value of 0.044. Colour bar represents t value in each voxel within the significant cluster. The MNI coordinates of the three slices are [3, 46, 6].
Navigation with MRI

Crux helicis
Target in depression: border between BA9 and BA 46 (Mylius et al. 2013)
● Activate left DLPFC with high frequency, e.g. 10 Hz – side effects with high energy
● Inhibit right DLPFC with low frequency, e.g. 1 Hz – efficacy also against anxiety (Diefenbach et al. 2016)
● Do both
● Theta burst stimulation with a robot – shorter sessions < 10 minutes
● Many sessions per day (Tor et al. 2016)
● Option to treat more than one indication per session, e.g. depression, chronic pain and tinnitus
10Hz

conventional rTMS

Patterend TMS
Theta Burst Stimulation (TBS)

200 ms

5 Hz repetition rate (Theta)
facilitating: iTBS: 2s on, 8s off, 20 Trains
inhibiting: cTBS: 40s on - 600 Pulses
Solutions for Robotic TMS
Discover in this brochure the key advantages of robot-assisted TMS
TABLE 1. Commonly used rTMS and TBS parameters in treating depression

<table>
<thead>
<tr>
<th>Parameters</th>
<th>rTMS</th>
<th>TBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-frequency rTMS</td>
<td>High-frequency rTMS</td>
</tr>
<tr>
<td>Intensity (motor threshold)</td>
<td>110% rMT</td>
<td>120% rMT</td>
</tr>
<tr>
<td>Frequency of stimulation</td>
<td>1 Hz</td>
<td>10 Hz</td>
</tr>
<tr>
<td>Interstimulus interval (ISI)</td>
<td>1 s</td>
<td>100 ms</td>
</tr>
<tr>
<td>Train duration</td>
<td>20 min</td>
<td>4 s</td>
</tr>
<tr>
<td>Intertrain interval (ITI)</td>
<td>–</td>
<td>25 s</td>
</tr>
<tr>
<td>Interblock interval (IBI)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of trains</td>
<td>–</td>
<td>75 trains</td>
</tr>
<tr>
<td>Total number of stimulus(^a)</td>
<td>1,200</td>
<td>3,000</td>
</tr>
<tr>
<td>Administration site</td>
<td>Right DLPFC</td>
<td>Left DLPFC</td>
</tr>
</tbody>
</table>

\(^a\)Total number of stimulus given per day may vary.

aMT/rMT, active/resting motor threshold; DLPFC, dorsolateral prefrontal cortex; cTBS/iTBS, continuous/intermittent theta-burst stimulation; rTMS, repetitive transcranial magnetic stimulation.
Efficacy of rTMS in depression

- Good evidence → level A in Finland
- More than 20 meta-analyses: d has varied between 0.4 and 0.7
- In general, results are better in newer studies and with MRI-based navigation
ECT is more effective than rTMS in depression (Slotema et al. 2010)

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges' g</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eranti et al, 2007</td>
<td>-0.957</td>
<td>.002</td>
</tr>
<tr>
<td>Pridmore et al, 2000</td>
<td>-0.420</td>
<td>.263</td>
</tr>
<tr>
<td>Grunhaus et al, 2000</td>
<td>-0.889</td>
<td>.006</td>
</tr>
<tr>
<td>Grunhaus et al, 2003</td>
<td>-0.147</td>
<td>.636</td>
</tr>
<tr>
<td>Janicak et al, 2002</td>
<td>-0.202</td>
<td>.630</td>
</tr>
<tr>
<td>Rosa et al, 2006</td>
<td>-0.102</td>
<td>.760</td>
</tr>
<tr>
<td>Weighted effect size, mean</td>
<td>-0.474</td>
<td>.004</td>
</tr>
</tbody>
</table>
Prediction of response

- Young patients (Aguirre et al. 2010) ← neuroplasticity
- Effective also for psychotic depression (Ray et al. 2011)
- Effective also for ECT-refractory patients (Connolly et al. 2012)
- Ekstraverision predicts good response (Berlim et al. 2013)
rTMS in psychotic depression (N = 45, 67 % of patients were psychotic, Ray et al. 2011)
Maintenance treatment of depression

- Steady maintenance: one session per week, fortnightly sessions probably insufficient (Benadhira et al. 2017)
- Tapering down session frequency, c.f. ECT (Connolly et al. 2012)
- Clustered maintenance: 5 sessions during a weekend (Fitzgerald et al. 2012)
rTMS is more cost-effective than antidepressants in TRD (Nguyen and Gordon 2015)

Table 2 – Costs, effects, cost-effectiveness ratios, and net monetary benefit (2013–2014 AUD).

<table>
<thead>
<tr>
<th>Mean values</th>
<th>3 y (base case)</th>
<th>5 y (sensitivity analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antidepressant</td>
<td>rTMS</td>
</tr>
<tr>
<td>Total cost</td>
<td>$31,190</td>
<td>$31,003</td>
</tr>
<tr>
<td>Incremental total cost</td>
<td>–</td>
<td>-$187</td>
</tr>
<tr>
<td>Total QALYs</td>
<td>1.18</td>
<td>1.25</td>
</tr>
<tr>
<td>Incremental total QALYs</td>
<td>–</td>
<td>0.07</td>
</tr>
<tr>
<td>Cost/QALY</td>
<td>$26,432</td>
<td>$24,803</td>
</tr>
<tr>
<td>Incremental cost per QALY</td>
<td>–</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

AUD, Australian dollar; QALY, quality-adjusted life-year; rTMS, repetitive transcranial magnetic stimulation.
Ketamine in the treatment of depression

- Non-competitive NMDA-antagonist: developed as an anaesthetic
- Fastest and most effective short-term treatment for major depression
- Activity of AMPA-receptors increases $\rightarrow$ mTOR-pathway activates $\rightarrow$ synaptic activity and number of dendritic spines increases $\rightarrow$ enhancement of brain plasticity (Maeng et al. 2008, Li et al. 2010, Tizabi et al. 2012, Cornwell et al. 2012, Zunszain et al. 2013)
- Used as a club-drug
- Most common method: racemic ketamine 0.5 mg/kg/45 min i.v. once a week
- Short-term treatment (< 2 weeks) is evidence-based, long-term treatment is still experimental
- Reliefs pain
- APA consensus statement (Sanacora et al. 2017)
Ketamine once vs. twice a week

A
Masennuksen voimakkuus (%)

B
Masennuksen voimakkuus (%)

Päivät infuusion jälkeen

Infuusio

Infuusio

Infuusio

Infuusio
FIGURE 2. Response Rates Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam

- Ketamine (N=47)
- Midazolam (N=25)
Ketamine in the treatment of depression 2

- Effective also for ECT-refractory patients (Ibrahim ym. 2011)
- Long-term safety in unknown - our hospital has limited length of treatments to 3 months
- In apes, ketamine is neurotoxic in doses > 10 mg/kg (Slikker et al. 2007)
- Ketamine abusers have impaired memory (Morgan et al. 2009) and decline of grey-matter volume in DLPFC (Liao et al. 2011)
- Main contraindications: previous schizophreniform psychosis, abuse history, blood in urine, risk of pregnancy, psychological incapacity to stand cessation of treatment
Ketamine-dependence and grey-matter decline: particularly right middle frontal gyrus (Liao et al. 2011)
Combinations

- Many possibilities, e.g. venlafaxine + mirtazapine + bupropion + psychotherapy + 1 Hz rTMS + ketamine (rTMS and ketamine on different days)
- Various combinations may have long-term additive effects (Castren 2013)
- Ketamine anaesthesia does not increase the efficacy of ECT (McGirr et al. 2017), but may boost the response (Li et al. 2017) – how about ECT and ketamine on separate days?
Single Ketamine infusion and escitalopram (Hu et al. 2015)
Ketamine anaesthesia does not boost ECT (McGirr et al. 2017)

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>P</th>
<th>Ketamine</th>
<th>Control</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdallah et al (2012)</td>
<td>-0.592</td>
<td>-1.536</td>
<td>0.352</td>
<td>0.219</td>
<td>9</td>
<td>9</td>
<td>7.81</td>
</tr>
<tr>
<td>Shams Alizadeh et al (2015)</td>
<td>-0.484</td>
<td>-1.098</td>
<td>0.130</td>
<td>0.123</td>
<td>22</td>
<td>20</td>
<td>9.91</td>
</tr>
<tr>
<td>Anderson et al (in press)</td>
<td>-0.709</td>
<td>-1.193</td>
<td>-0.225</td>
<td>0.004</td>
<td>33</td>
<td>37</td>
<td>10.71</td>
</tr>
<tr>
<td>Jarventausta et al (2013)</td>
<td>-0.023</td>
<td>-0.696</td>
<td>0.650</td>
<td>0.947</td>
<td>16</td>
<td>18</td>
<td>9.53</td>
</tr>
<tr>
<td>Kuscu et al (2015)</td>
<td>0.489</td>
<td>-0.047</td>
<td>1.024</td>
<td>0.074</td>
<td>40</td>
<td>21</td>
<td>10.40</td>
</tr>
<tr>
<td>Loo et al (2012)</td>
<td>0.129</td>
<td>-0.421</td>
<td>0.679</td>
<td>0.645</td>
<td>26</td>
<td>25</td>
<td>10.31</td>
</tr>
<tr>
<td>Rybakowski et al (2016)</td>
<td>0.240</td>
<td>-0.381</td>
<td>0.862</td>
<td>0.449</td>
<td>30</td>
<td>15</td>
<td>9.86</td>
</tr>
<tr>
<td>Salehi et al (2015)</td>
<td>0.466</td>
<td>0.152</td>
<td>0.780</td>
<td>0.004</td>
<td>80</td>
<td>80</td>
<td>11.60</td>
</tr>
<tr>
<td>Yoosefi et al (2014)</td>
<td>0.456</td>
<td>-0.261</td>
<td>1.172</td>
<td>0.212</td>
<td>17</td>
<td>14</td>
<td>9.25</td>
</tr>
<tr>
<td>Zhong et al (2016)</td>
<td>1.608</td>
<td>1.111</td>
<td>2.105</td>
<td>0.000</td>
<td>60</td>
<td>30</td>
<td>10.63</td>
</tr>
</tbody>
</table>

Fig. 2  Change in clinician-administered depression rating scores. SMD, standardised mean difference.