Appendix 2

Treatment of depression with transcranial magnetic stimulation using an H-coil (dTMS) – An HTA report, report 318 (2020)

Appendix 2 Characteristics of included studies

Author Year Reference Country Study design	Setting Recruitment Population Inclusion criteria Follow up	Intervention Participants Drop-outs	Control Participants Drop-outs	Outcomes	Comments Risk of bias
Levkovitz el al 2015 [1] Multinational RCT	**Setting** 20 medical centres in USA, Canada, Germany and Israel **Recruitment** Advertisements and physician referrals **Population** Outpatients with MDD according to DSM-IV n=212 **Inclusion criteria** Free from antidepressant medication following wash-out period (1–2 weeks) Had failed 1–4 treatments with antidepressant medication CGI-S ≥4 and HDRS-21 ≥20 Age 22–68 years	**Intervention** dTMS with H1-coil **Dose** Acute: 4 weeks with 5 sessions per week Maintenance: 12 weeks with 2 sessions per week 2 sec pulse 18 Hz 120% of MT, followed by 20 sec pause x 55 at each session (=1980 pulses) **Participants** n=101 (ITT) **Age**[a] 45.1±11.7 years **Baseline HDRS-21 score**[a] 23,5±4,3 **Drop-outs** 19 patients (19%) from baseline to week 5 58 patients (57%) from baseline to week 16	**Control** Sham dTMS **Dose** Same as for the intervention group **Participants** n=111 (ITT) **Age**[a] 47.6±11.6 years **Baseline HDRS-21 score**[a] 23,4±3,7 **Drop-outs** 34 patients (31%) from baseline to week 5 83 patients (75%) from baseline to week 16	*Analysed after 5 weeks of treatment* **Change in HDRS-21 from baseline**[b,c] I: –6.17 (–7.78 to –4.55) C: –3.94 (–5.58 to –2.29) p=0.058 **Response rate**[d,e] I: 34/101 (33.7%) C: 23/111 (20.7%) p=0.034 **Remission rate**[f,e] I: 28/101 (27.7%) C: 16/111 (14.4%) p=0.017 *Analysed after 16 weeks of treatment (maintenance)* **Change in HDRS-21 from baseline**[g,h] I: –8,04 (–9.91 to –6.16) C: –6.31 (–7.99 to –4.62) p=0.104	Company sponsored study **Risk of bias** Moderate

				Response rate[i,e] I: 39/101 (38.6%) C: 27/111 (24.3%) p=0.025 **Remission rate**[j,e] I: 28/101 (27.7%) C: 23/111 (20.7%) p=0.234	
Tavares et al 2017 [2] Brazil RCT	**Setting** 1 hospital in Brazil **Recruitment** Advertisements, physician referrals and patients from academic mood disorder clinics **Population** Bipolar disorder type I or II in acute depressive episode according to DSM-IV n=50 **Inclusion criteria** Free from antidepressant medication following wash-out period (4 weeks) Had failed ≥2 pharmacological	**Intervention** dTMS with H1-coil **Dose** Acute: 4 weeks with 5 sessions per week 2 sec pulse 18 Hz 120% of MT, followed by 20 sec pause x 55 at each session (=1980 pulses) **Participants** n=25 (ITT) **Age**[a] 43.5±12 years **Baseline HDRS-17 score**[a] 25.8±5.25 **Drop-outs** 5 patients (20%)	**Control** Sham dTMS **Dose** Same as for the intervention group **Participants** n=25 (ITT) **Age**[a] 41.2±8.9 years **Baseline HDRS-17 score**[a] 25.32±3.76 **Drop-outs** 2 patients (8%)	*Analysed after 4 weeks of treatment* **Change in HDRS-17 from baseline**[k] I: –11.72 C: –6.36 **Response rate**[l] I: 12/25 (48%) C: 6/25 (24%) p=0.08 **Remission rate**[m] I: 7/25 (28%) C: 4/25 (16%) p=0.31 *Analysed 4 weeks after end of treatment (follow-up)* **Change in HDRS-17 from baseline** I: –9.32	Company sponsored study **Risk of bias** Low

	treatments for BD At least moderate depression HDRS-17 >17 Age 18–65 years **Follow-up** 4 weeks after end of treatment			C: –6.08 p=0.046[n] **Response rate[l]** I: 8/25 (32%) C: 6/25 (24%) p=0.63 **Remission rate[m]** I: 6/25 (24%) C: 6/25 (24%) p=1	
Kaster et al 2018 [3] Canada RCT	**Setting** 1 hospital in Canada **Recruitment** Outpatients **Population** Outpatients with MDD according to DSM-IV 60–85 years old n=58 **Inclusion criteria** Stable dosages of psychotropic medications for ≥4 weeks Had failed ≥1 adequate or ≥2 inadequate antidepressant trials according to ATHF	**Intervention** dTMS with H1-coil (initially H1L-helmet) **Dose** Acute: 4 weeks with 5 sessions per week Maintenance: For those with remission at 4 weeks, 2 weeks with 2 sessions per week 2 sec pulse 18 Hz 120% of MT, followed by 20 sec pause x 167 at each session (=6012 pulses) **Participants** n=30 (allocated) n=25 (ITT: H1-coil) **Age[a]** 65.0±5.5 years	**Control** Sham dTMS **Dose** Same as for the intervention group **Participants** n=28 (allocated) n=27 (ITT: H1-coil) **Age[a]** 65.4±5.5 years	*Analysed after 4 weeks of treatment* **Change in HDRS-24 from baseline** I: –11.12 C: –9.89 p=0.438[p] **Response rate[q]** I: 11/25 (44%) C: 5/27 (18.5%) p<0.05 **Remission rate[r]** (primary) I: 10/25 (40%) C: 4/27 (14.8%) p<0.05	Company sponsored study Intervention was changed during study **Risk of bias** Moderate

	HDRS-24 ≥22 MMSE[o] ≥26	**Baseline HDRS-24 score[a]** 25.8±4.0 **Drop-outs** 5 patients treated with H1L helmet (not included in ITT) 5 patients treated with H1-coil discontinued treatment	**Baseline HDRS-24 score[a]** 27.6±4.1 **Drop-outs** 1 patient treated with sham H1L helmet (not included in ITT) 0 patients treated with sham H1 coil discontinued treatment		
Filipcic et al 2019 [4] Croatia RCT	**Setting** 1 hospital in Croatia **Recruitment** Physician referrals **Population** MDD according to DSM-5 n=228 **Inclusion criteria** At least one prior disease episode Unchanged psychopharmacological treatment for 4 weeks Age: 20–70 years	**Intervention** dTMS with H1-coil (plus standard pharmacotherapy) **Dose** Acute: 4 weeks with 5 sessions per week 2 sec pulse 18 Hz 120% of MT, followed by 20 sec pause x 55 at each session (=1980 pulses) **Participants** n=72 (ITT) **Age[s]** 50 (44–60) years	**Control** rTMS with figure-8-coil (plus standard pharmacotherapy) or Only standard pharmacotherapy **Dose (figure-8-coil)** 4 weeks with 5 sessions per week 4 sec pulse 10 Hz 120% of MT, followed by 26 sec pause x 75 at each session **Participants** Figure-8-coil: n=75 (ITT) Standard therapy: n=81 (ITT) **Age[s]**	*Analysed after 4 weeks of treatment* **Change in HDRS-17 from baseline** I: –10 C (Figure-8-coil): –7 C (Standard therapy): –3 I vs Figure-8-coil: p=0.05[t] I vs Standard therapy: p<0.001[t] **Response rate[l]** I: 48/72 (66.7%) C (Figure-8-coil): 33/75 (44%) C (Standard therapy): 19/81 (23,5%) I vs Figure-8-coil: p=0.04[u] I vs Standard therapy: p<0.001[u]	Post-hoc review indicated that all patients had failed at least two previous adequately given antidepressant treatments without response. **Risk of bias** Differentiated risk for bias depending on control group. ***Figure-8-coil*** Low risk of bias ***Standard therapy*** Risk for differences in unspecific effects due to differences in for example number of

		Baseline HDRS-17 score[a] 17±5.4 **Drop-outs** 7 patients (9.7%)	Figure-8-coil: 51 (42–59) years Standard therapy: 53 (48–61) years **Baseline HDRS-17 score**[a] Figure-8-coil: 17±5.4 Standard therapy: 18±6.2 **Drop-outs** Figure-8-coil: 3 (4%) Standard therapy: 9 (11.1%)	**Remission rate**[m] I: 43/72 (59.7%) C (Figure-8-coil): 32/75 (42.7%) C (Standard therapy): 9/81 (11.1%) I vs Figure-8-coil: p=0.17[u] I vs Standard therapy: p<0.001[u]	visits High risk of bias
Matsuda et al 2020 [5] Japan RCT	**Setting** 1 hospital in Japan **Recruitment** Not described **Population** MDD (37.5%) or bipolar disorder (62.5%) type I or II, in acute depressive episode according to DSM-5 Office workers on administrative leave for treatment-resistant depression n=40 **Inclusion criteria** Unchanged medication	**Intervention** dTMS with H1-coil **Dose** Acute: 4 weeks with 5 sessions per week. For those without remission at 4 weeks, 2 more weeks with 5 sessions per week. 2 sec pulse 18 Hz 120% of MT, followed by 20 sec pause x 55 at each session (=1980 pulses) **Participants** n=20 (ITT) **Age**[a] 43.4±5.5 years	**Control** Sham dTMS **Dose** Same as for the intervention group **Participants** n=20 (ITT) **Age**[a] 45.2±7.0 years	*Analysed after 4 weeks of treatment* **Change in HDRS-21 from baseline**[v] I: –4.45 (–7.95 to –0.96) C: –0.22 (–3.74 to 3.30) p=0,091[s] **Response rate**[d] I: 2/20 (10%) C: 3/20 (15%) p=0.633 **Remission rate**[w] I: 2/20 (10%) C: 3/20 (15%) p=0.633	Primary analysis was done after 6 weeks although treatment given after 4 weeks varied depending on response to treatment. Results after 4 weeks are regarded as the most reliable and are reported here. **Risk of bias** Moderate

	for at least 4 weeks Treatment-resistant Moderate to severe depression, HDRS-21 ≥20 Age 25–75 years	**Baseline HDRS-21 score**[a] 19.4±8.2 **Depression characteristics** Unipolar depression: 40% Bipolar depression: 60% **Drop-outs** 2 patients (10%)	**Baseline HDRS-21 score**[a] 20.5±4.1 **Depression characteristics** Unipolar depression: 30% Bipolar depression: 65% Not specified: 5% **Drop-outs** 0 patients (0%)		

ATHF = Antidepressant Treatment History Form; **C** = Control; **CGI-S** = Clinical Global Impression – Severity scale; **DSM** = Diagnostic and Statistical Manual of Mental Disorders; **dTMS** = deep Transcranial Magnetic Stimulation; **HDRS** = Hamilton Depression Rating Scale; **I** = Intervention; **ITT** = Intention to treat; **MDD** = Major depressive disorder; **MT** = Motor Threshold; **MMSE** = Mini Mental Status Exam; **p** = p-value; **RCT** = Randomised controlled trial; **rTMS** = repetitive Transcranial Magnetic Stimulation; **vs** = versus

[a] Mean ± SD.
[b] Slope of change from baseline to week 5 from a repeated measures analysis of covariance.
[c] The authors excluded patients from the ITT analysis that did not have a post baseline measurement. In this analysis n=92 for the intervention group and n=101 for the control group (personal communication by e-mail with Abraham Zangen at Ben Gurion University in Israel on 18th of August 2020).
[d] Defined as a reduction of at least 50% in HDRS-21 compared to baseline.
[e] Data reported here is based on the ITT population as it was defined in the paper (i.e. all subjects who received at least one treatment session). The data reported in the paper does not correspond to the ITT population as defined in the paper, as patients that did not have a post baseline measurement (i.e. dropped out in the first week) were excluded (personal communication by e-mail with Abraham Zangen at Ben Gurion University in Israel on 18th of August 2020).
[f] Defined as HDRS-21 <10.
[g] Slope of change from baseline to last observed value (LOV) from a repeated measures analysis of covariance.
[h] The authors excluded patients from the ITT analysis that did not have a post baseline measurement. In this analysis n=96 for the intervention group and n=104 for the control group (personal communication by e-mail with Abraham Zangen at Ben Gurion University in Israel on 18th of August 2020).
[i] Defined as a reduction of at least 50% in HDRS-21 at the last observed value (LOV) compared to baseline.
[j] Defined as HDRS-21 <10 at the last observed value (LOV).
[k] No p-value was reported for the difference in change in HDRS score from baseline to week 4 between treatment groups.
[l] Defined as a reduction of at least 50% in HDRS-17 compared to baseline.
[m] Defined as HDRS-17 ≤7.
[n] The p-value is derived from a mixed effects linear regression for difference in change in HDRS-21 score from baseline to week 8 between treatment groups (time x group interaction).

[o] Mini Mental Status Exam.
[p] The p-value is derived from a mixed effects model for difference in change in HDRS-21 score from baseline to week 4 between treatment groups (time x group interaction).
[q] Defined as a reduction of at least 50% in HDRS-24 compared to baseline on 2 consecutive weeks.
[r] Defined as both HDRS-24 ≤10 and ≥60% reduction from baseline on 2 consecutive weeks.
[s] Median (interquartile range).
[t] The p-value is derived from an analysis of covariance model for difference in change in HDRS-21 score from baseline to week 4 between treatment groups.
[u] The p-value is derived from a multivariate binary logistic regression that controlled for possible confounders.
[v] The authors excluded patients from the ITT analysis that dropped out from the treatment due to side effects. In the analysis n=18 in the intervention group and n=20 in the control group (personal communication by e-mail with Yuki Matsuda at Jikei University School of Medicine in Japan on 3rd of June 2020).
[w] Defined as HDRS-21 ≤9.

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