Bilaga 1-6

Behandling av depression med transkraniell magnetstimulering med H-spole (dTMS) – en uppdatering, rapport 318 (2020)

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Bilaga 2

Behandling av depression med transkraniell magnetstimulering med H-spole (dTMS) – en uppdatering, rapport 318 (2020)

Bilaga 2 Granskningsmall för kvalitetsbedömning

Bedömning av randomiserad studie (ITT)

UPPDATERAD 2019-04-26

Referens (författare, år): _____

Utfall: _____

Granskare: _____

Övergripande risk för systematisk snedvridning av resultaten (risk för bias)					
Låg ❑		Måttlig ❑		Hög ❑	
Om möjligt: Vilken är riktningen på bias för detta utfall?	Gynnar intervention ❑	Gynnar kontroll ❑	Mot noll ❑	Från noll ❑	Går ej att bedöma ❑
Kommentarer:					

1. Randomisering

Risk för bias från randomiseringen bedöms som:			**Låg** ❑	**Måttlig** ❑	**Hög** ❑
			Motivering: se stödfrågorna nedan		
Bedömer du att..?	**Ja**	**Troligen ja**	**Troligen nej**	**Nej**	**Information saknas**
1.1 gruppindelningen var randomiserad med en lämplig metod?	❑	❑	❑	❑	❑
1.2 blivande grupptillhörighet inte kunde förutses, den var okänd tills deltagarna delats in (concealed allocation sequence)?	❑	❑	❑	❑	❑
1.3 det fanns väsentliga obalanser vid baslinjen som tyder på att randomiseringen inte fungerat?	❑	❑	❑	❑	❑
Om möjligt: Vilken är riktningen på bias för utfallet?	Gynnar intervention ❑	Gynnar kontroll ❑	Mot noll ❑	Från noll ❑	Går ej att bedöma ❑

2. Avvikelser från planerade interventioner

Risk för bias från avvikelser från planerade interventioner bedöms som:			**Låg** ❑	**Måttlig** ❑	**Hög** ❑
			Motivering: se stödfrågorna nedan		
Bedömer du att..?	**Ja**	**Troligen ja**	**Troligen nej**	**Nej**	**Information saknas**
2.1 deltagarna kände till vilken intervention de tilldelats under studiens gång?	❑	❑	❑	❑	❑
2.2 behandlarna kände till vilka interventioner deltagarna tilldelats under studiens gång?	❑	❑	❑	❑	❑
Besvara 2.3 om du svarat "Ja", "Troligen ja" eller "Information saknas" på 2.1. eller 2.2.					
2.3 kännedom om studien och gruppindelningen kunde leda till avvikelser som var obalanserade mellan grupperna (t.ex. förändringar i övrig vård eller avvikelser från klinisk praxis)?	❑	❑	❑	❑	❑
Besvara 2.4 om du svarat "Ja" eller "Troligen ja" på 2.3.					
2.4 avvikelserna var obalanserade mellan grupperna, och detta påverkade utfallet?	❑	❑	❑	❑	❑
2.5 flera av deltagarna analyserades i en annan grupp än den de randomiserades till, eller att deltagare exkluderades från analysen – och detta påverkade sannolikt utfallet?	❑	❑	❑	❑	❑
Om möjligt: Vilken är riktningen på bias för utfallet?	Gynnar intervention ❑	Gynnar kontroll ❑	Mot noll ❑	Från noll ❑	Går ej att bedöma ❑

3. Bortfallet

Risk för bias från bortfall bedöms som:			**Låg** ❑	**Måttlig** ❑	**Hög** ❑
			Motivering: se stödfrågorna nedan		
Bedömer du att..?	**Ja**	**Troligen ja**	**Troligen nej**	**Nej**	**Information saknas**
3.1 resultat redovisades för alla eller nästan alla deltagare?	❑	❑	❑	❑	❑
Besvara 3.2 om du svarat "Nej", "Troligen nej" eller "Information saknas" på 3.1.					
3.2 det finns evidens som stödjer att resultaten är robusta trots bortfallet?	❑	❑	❑	❑	❑
Besvara 3.3 om du svarat "Nej" eller "Troligen nej" på 3.2.					
3.3 bortfallet kan vara relaterat till utfallsmåttet?	❑	❑	❑	❑	❑
Besvara 3.4 om du svarat "Ja", "Troligen ja" eller "Information saknas" på 3.3.					
3.4 såväl bortfallet som orsaker till bortfallet var likartat mellan grupperna?	❑	❑	❑	❑	❑
Om möjligt: Vilken är riktningen på bias för utfallet?	Gynnar intervention ❑	Gynnar kontroll ❑	Mot noll ❑	Från noll ❑	Går ej att bedöma ❑

4. Mätning av utfallet

Risk för bias från mätning av utfallet bedöms som:			**Låg** ❑	**Måttlig** ❑	**Hög** ❑
			Motivering: se stödfrågorna nedan		
Bedömer du att..?	**Ja**	**Troligen ja**	**Troligen nej**	**Nej**	**Information saknas**
4.1 metoden för datainsamling var olämplig?	❑	❑	❑	❑	❑
4.2 datainsamlingen skilde sig åt mellan grupperna?	❑	❑	❑	❑	❑
4.3 de som mätte utfallet var medvetna om vilken intervention deltagarna fått?	❑	❑	❑	❑	❑
Besvara 4.4 om du svarat "Ja", "Troligen ja" eller "Information saknas" på någon av frågorna ovan.					
4.4 bedömningen med stor sannolikhet påverkades av detta?	❑	❑	❑	❑	❑
Om möjligt: Vilken är riktningen på bias för utfallet?	Gynnar intervention ❑	Gynnar kontroll ❑	Mot noll ❑	Från noll ❑	Går ej att bedöma ❑

5. Rapportering

Risk för bias från rapportering bedöms som:			**Låg** ❑	**Måttlig** ❑	**Hög** ❑
			Motivering: se stödfrågorna nedan		
Bedömer du att..?	**Ja**	**Troligen ja**	**Troligen nej**	**Nej**	**Information saknas**
5.1 analyserna var genomförda enligt en plan som publicerats innan utfallsdata var tillgängliga?	❑	❑	❑	❑	❑
5.2 de rapporterade resultaten har valts ut från flera sätt att mäta utfallet (t.ex. olika skalor, tidpunkter)?	❑	❑	❑	❑	❑
5.3 de rapporterade resultaten har valts ut från olika analyser av samma utfall?	❑	❑	❑	❑	❑

Om möjligt: Vilken är riktningen på bias för utfallet?	Gynnar intervention ❑	Gynnar kontroll ❑	Mot noll ❑	Från noll ❑	Går ej att bedöma ❑

6. Jäv/intressekonflikter (kan rapporteras narrativt)

	Ja	**Nej**	**Kommentar**
Deklarerar författarna att de saknar finansiella intressen som kan påverka utfallet?	❑	❑	❑
Deklarerar författarna att de saknar andra bindningar som kan påverka utfallet?	❑	❑	❑

Om möjligt: Vilken är riktningen på bias för utfallet?	Gynnar intervention ❑	Gynnar kontroll ❑	Mot noll ❑	Från noll ❑	Går ej att bedöma ❑

Bilaga 3

Behandling av depression med transkraniell magnetstimulering med H-spole (dTMS) – en uppdatering, rapport 318 (2020)

Bilaga 3 Tabell över inkluderade studier/ Appendix 3 Table 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 **Response rate**[i,e] I: 39/101 (38.6%)	Company sponsored study **Risk of bias** Moderate

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
				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 treatments for BD At least moderate depression HDRS-17 >17	**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**	Company sponsored study **Risk of bias** Low

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
	Age 18–65 years **Follow-up** 4 weeks after end of treatment			I: –9.32 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	**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)	**Control** Sham dTMS **Dose** Same as for the intervention group **Participants** n=28 (allocated) n=27 (ITT: H1-coil)	*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%)	Company sponsored study Intervention was changed during study **Risk of bias** Moderate

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
	Had failed ≥1 adequate or ≥2 inadequate antidepressant trials according to ATHF HDRS-24 ≥22 MMSE[o] ≥26	**Age**[a] 65.0±5.5 years **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	**Age**[a] 65.4±5.5 years **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	p<0.05	
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)	**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)	*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]	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 visits

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
		Age[s] 50 (44–60) years **Baseline HDRS-17 score**[a] 17±5.4 **Drop-outs** 7 patients (9.7%)	**Age**[s] 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%)	I vs Standard therapy: p<0.001[u] **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]	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**	**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

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
	Unchanged medication 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

References

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3. Kaster TS, Daskalakis ZJ, Noda Y, Knyahnytska Y, Downar J, Rajji TK, et al. Efficacy, tolerability, and cognitive effects of deep transcranial magnetic stimulation for late-life depression: a prospective randomized controlled trial. Neuropsychopharmacology 2018;43:2231-8.
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5. Matsuda Y, Kito S, Igarashi Y, Shigeta M. Efficacy and Safety of Deep Transcranial Magnetic Stimulation in Office Workers with Treatment-Resistant Depression: A Randomized, Double-Blind, Sham-Controlled Trial. Neuropsychobiology 2020;79:208-13.

Bilaga 4

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Bilaga 4 Risk för biasbedömning av inkluderade studier/ Appendix 4 Risk of bias chart

Effect directly after end of treatment

Author Year Reference	Comparison	Randomisation	Deviation from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall bias	Comments
Levkovitz et al 2015 [1]	dTMS compared to sham	Low	Low	Low	Low	Moderate	Moderate	Time point for effect measure changed from 4 weeks to 5 weeks in the protocol in clinicaltrials.gov close to publication of the study. Recruitment partly through advertisement. Brainsway involved in study
Tavares et al 2017 [2]	dTMS compared to sham	Low	Low	Low	Low	Low	Low	Recruitment partly through advertisement. Brainsway involved in study
Kaster et al 2018 [3]	dTMS compared to sham	Moderate	Low	Low	Low	Moderate	Moderate	Protocol changed during the study both regarding type of intervention (H1L helmet versus H1 coil) and the primary efficacy measure (different definition of remission in clinicaltrials.gov compared to the publication). Small study that was stopped prematurely with some differences at the baseline that can have affected the result in advantage of the intervention. Brainsway involved in study
Filipčić et al 2019 [4]	dTMS compared to	Low	Low	Low	Low	Low	Low	Only the rater of the results was blinded. The patients and the clinician delivering the treatment

Author Year Reference	Comparison	Randomisation	Deviation from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall bias	Comments
	rTMS with figure-8-coil							were unblinded, but this is not thought to bias the results.
Filipčić et al 2019 [4]	dTMS compared to pharmaceutic treatment	Low	High	Low	Low	Low	High	Risk for unspecific differences in effect in the control group that only met clinicians at baseline and at 4 weeks compared to the intervention group that met clinicians 5 days a week for 4 weeks
Matsuda et al 2020 [5]	dTMS compared to sham	Low	Low	Moderate	Low	Moderate	Moderate	Excluded patients that dropped-out during the study from the analysis. No protocol found. Risk that the result after 6 weeks is chosen due to a significant result at that time point not seen at other time points.

Effect of maintenance treatment

Author Year Reference	Comparison	Randomisation	Deviation from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall bias	Comments
Levkovitz et al 2015 [1]	Maintenance treatment with dTMS compared to sham	Low	Low	High	Low	Moderate	High	Large proportion of the patients dropped out until end of maintenance treatment (57–75%)
Rapinesi et al 2015 [6]	Maintenance treatment with dTMS compared to no	High	High	-	-	-	High	Not clearly reported how randomisation was done. Study unblinded for patients and therapists.

Author Year Reference	Comparison	Randomisation	Deviation from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall bias	Comments
	maintenance treatment							

References

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Bilaga 5

Behandling av depression med transkraniell magnetstimulering med H-spole (dTMS) – en uppdatering, rapport 318 (2020)

Bilaga 5 Exkluderade studier/Excluded studies

Studies excluded due to relevance/Studier som bedömts som inte relevanta

Study/Studie	Reason for exclusion/ Exklusionsorsak
Filipčić I, Šimunović Filipčić I, Sučić S, Milovac Ž, Gereš N, Matić K, et al. A pilot investigation of accelerated deep transcranial magnetic stimulation protocols in treatment-resistant depression. Eur Arch Psychiatry Clin Neurosci 2020.	Study design – not a real RCT as treatment groups were analysed at different time points after baseline
Isserles M, Rosenberg O, Dannon P, Levkovitz Y, Kotler M, Deutsch F, et al. Cognitive-emotional reactivation during deep transcranial magnetic stimulation over the prefrontal cortex of depressive patients affects antidepressant outcome. J Affect Disord 2011;128:235-42.	Control - not relevant control group
Kaur J, Mania I. Deep transcranial magnetic stimulation (dTMS) for treatment of major depressive disorder (MDD) status post-surgical removal of medulloblastoma: A case report of safety. Brain Stimul 2019;12:1061-2.	Study design – Case report of side effects in one patient

Studies with high risk of bias/Studier med hög risk för bias

Study/Studie	Reason for exclusion/ Exklusionsorsak
Rapinesi C, Bersani FS, Kotzalidis GD, Imperatori C, Del Casale A, Di Pietro S, et al. Maintenance Deep Transcranial Magnetic Stimulation Sessions are Associated with Reduced Depressive Relapses in Patients with Unipolar or Bipolar Depression. Front Neurol 2015;6:16.	High risk of bias - Not clearly reported how randomization was done. Study unblinded for patients and therapists

Bilaga 6

Behandling av depression med transkraniell magnetstimulering med H-spole (dTMS) – en uppdatering, rapport 318 (2020)

Bilaga 6 Biverkningar vid dTMS

Mindre allvarliga biverkningar

Biverkning	Behandling	Levkovitz et al [1] 2015	Levkovitz et al [2] 2013 FDA-rapport	Tavares et al [3] 2017*	Kaster et al [4] 2018	Filipcic et al [5] 2019
Smärta på stimuleringsstället/ Skalpsmärta	dTMS sham rTMS	5/101 (5 %) 0/111 (0 %)[a]	27/111 (24,3 %) 1/122 (0,8 %)[b]	5/25 (20 %) 0/25 (0 %)[e]	4/25 (16 %) 0/27 (0 %)[f]	5/69 (7,2 %) – 0/74 (0 %)
Obehag på stimuleringsstället/ Brännande känsla	dTMS sham rTMS	3/101 (3 %) 2/111 (1,8 %)	21/111 (18,9 %) 5/122 (4,1 %)[c]	2/25 (8 %) 2/25 (8 %)		3/69 (4,3 %) – 1/74 (1,4 %)
Huvudvärk	dTMS sham rTMS	27/101 (26,7 %) 21/111 (18,9 %)	51/111 (45,9 %) 44/122 (36,1 %)	9/25 (36 %) 10/25 (40 %)	14/25 (56 %) 10/27 (37 %)	20/69 (29 %) 3/80 (3,8 %)[$] 15/74 (20,3 %)
Muskelryckningar	dTMS sham rTMS	2/101 (2 %) 0/111 (0 %)	7/111 (6,3 %) 2/122 (1,6 %)			8/69 (11,6 %) 0/80 (0 %)[$] 0/74 (0 %)
Käksmärta	dTMS sham rTMS		11/111 (9,9 %) 1/122 (0,8 %)[d]			8/69 (11,6 %) 0/80 (0 %)[$] 0/74 (0 %)
Sömnlöshet	dTMS sham rTMS	2/101 (2 %) 4/111 (3,6 %)	8/111 (7,2 %) 9/122 (7,4 %)			5/69 (7,2 %) 4/80 (5 %)[$] 5/74 (6,8 %)
Ångest	dTMS sham rTMS	– 2/111 (1,8%)	6/111 (5,4 %) 9/122 (7,4 %)		0/25 (0 %) 1/27 (3,7 %)	0/69 (0 %) 2/80 (2,5 %)[$] 1/74 (1,4 %)
Tandsmärta	dTMS sham		3/111 (2,7 %) 2/122 (1,6 %)		0/25 (0 %) 1/27 (3,7 %)	
Illamående	dTMS sham rTMS				1/25 (4 %) 1/27 (3,7 %)	0/69 (0 %) 1/80 (1,3 %)[$] 0/74 (0 %)
Ögonsmärta	dTMS sham		2/111 (1,8 %) 4/122 (3,3 %)			
Ryggsmärta	dTMS sham	2/101 (2 %) 3/111 (2,7 %)				

Biverkning	Behandling	Levkovitz et al [1] 2015	Levkovitz et al [2] 2013 FDA-rapport	Tavares et al [3] 2017*	Kaster et al [4] 2018	Filipcic et al [5] 2019
Nacksmärta	dTMS sham			6/25 (24 %) 8/25 (32 %)		
Klagomål på hörsel	dTMS sham			5/25 (20 %) 2/25 (8 %)		
Koncentrationssvårig-heter	dTMS sham			6/25 (24 %) 5/25 (20 %)		
Infektion i övre luftvägarna	dTMS sham		9/111 (8,1 %) 7/122 (5,7 %)			
Allergi	dTMS sham		6/111 (5,4 %) 3/122 (2,5 %)			
Nasofaryngit	dTMS sham				1/25 (4 %) 0/27 (0 %)	
Bihåleinflammation	dTMS sham				1/25 (4 %) 0/27 (0 %)	
Aftös stomatit (sår i munnen)	dTMS sham				1/25 (4 %) 0/27 (0 %)	
Hornhinneerosion	dTMS sham				1/25 (4 %) 0/27 (0 %)	
Hudinflammation	dTMS sham				1/25 (4 %) 0/27 (0 %)	
Yrsel	dTMS sham rTMS					4/69 (5,8 %) 1/80 (1,3 %)[$] 2/74 (2,7 %)
Trötthet (fatigue)	dTMS sham rTMS					0/69 (0 %) 2/80 (2,5 %)[$] 0/74 (0 %)

dTMS = deep Transcranial Magnetic Stimulation; **sham** = behandling med overksam spole; **rTMS** = repetitive Transcranial Magnetic Stimulation med figur-8-spole

[a] p=0,02

[b] p<0,0001

[c] p=0,0003

[d] p=0,0017

[e] p=0,05

[f] p<0,05

* I gruppen som får behandling med overksam spole ingår 25 individer i studien, men då procent individer med biverkningar beräknas i studien utgår man från 24. Eftersom det saknas förklaring till detta utgår vi från att det skulle ha varit 25 i denna grupp.

[$] Deltagarna fick ingen behandling med overksam spole utan enbart läkemedelsbehandling i denna studie. Biverkningar för dessa individer har därför inte inkluderats i vår sammanställning över biverkningar med behandling med overksam spole.

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