COCHRANE CORNER

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Pharmacological, Psychological, and Noninvasive Brain Stimulation Interventions for Treating Depression After Stroke

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pepression is common after stroke. This substantive update including new and combination interventions expands on our previous *Cochrane Reviews* published in 2004 and updated in 2008.

SEARCH METHODS

We searched electronic databases from inception to August 2018, clinical trial registers, conference proceedings, and contacted study authors.

SELECTION CRITERIA

Randomized controlled trials comparing (1) pharmacological interventions with placebo; (2) noninvasive brain stimulation with sham stimulation/usual care; (3) psychological therapy with usual care/attention control; (4) pharmacological and psychological therapy with pharmacological intervention and usual care/attention control; and (5) noninvasive brain stimulation and pharmacological intervention with pharmacological intervention and sham stimulation/usual care; to treat depression. Four comparisons are not reported because we found no trials.

RESULTS

Forty-nine trials (56 comparisons) with 3342 participants. Data were available for intervention (1) with 20

comparisons; (2) with 8; (3) with 16; (4) with 2; and (5) with 10 comparisons.

We have very little confidence in the following results due to the methodological limitations of many of the included trials.

Pharmacological interventions may decrease the number of people with diagnosable depression (risk ratio [RR], 0.70 [95% CI, 0.55–0.88]; 8 trials, 1025 participants, Figure), and with <50% reduction in depression scale scores at end of treatment (RR, 0.47 [95% CI, 0.32–0.69]; 6 trials, 511 participants) compared with placebo. There was an increase in adverse events related to the central nervous system (RR, 1.55 [95% CI, 1.12–2.15]; 5 trials, 488 participants) and gastrointestinal adverse events (RR, 1.62 [95% CI, 1.19–2.19]; 4 trials, 473 participant) compared with placebo.

Psychological therapy may decrease the number of people with diagnosable depression at end of treatment (RR, 0.77 [95% CI, 0.62–0.95]; 6 trials, 521 participants) with no evidence of death or adverse events compared with usual care/attention control.

There were no trials of noninvasive brain stimulation or combination therapies that reported the prevalence of diagnosable depression at end of treatment. Noninvasive brain stimulation interventions and combination therapies resulted in no deaths.

Key Words: depression = meta-analysis = randomized controlled trial = stroke = treatment

For Disclosures, see page xxx.

This paper is based on a Cochrane Review published in *The Cochrane Library*, 2020 (see www.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

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DISCUSSION

We lack confidence in the results for pharmacological and psychological interventions showing evidence of benefit and harm. The harm (in pharmacological trials) is concerning given the small number of trials in which harm was recorded and reported.¹

Large, well-designed trials, with proper collection of adverse events, for moderate/severe depression identified by standardized case-finding in the first 6 months after stroke are needed. In the absence of such trials, the best clinical advice is to restrict antidepressant prescription to people with persistent depression of moderate-severe intensity, and exercise caution in people with a history of falls, fracture or gastrointestinal bleeding.

ARTICLE INFORMATION

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Disclosures

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REFERENCES

 Allida S, Cox KL, Hsieh CF, Lang H, House A, Hackett ML. Pharmacological, psychological, and non-invasive brain stimulation interventions for treating depression after stroke. *Cochrane Database Syst Rev.* 2020;1:CD003437. doi: 10.1002/14651858.CD003437.pub4

	Pharmacotherapy Placebo					Risk Ratio	Risk Ratio	
Study or Subgroup					Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
1.1.1 Clinician intervi	ew/impressio	n (numb	er not im	proved	1)			
Ohtomo 1991	52	150	65	135	17.9%	0.72 [0.54, 0.95]		
Subtotal (95% CI)		150		135	17.9%	0.72 [0.54, 0.95]	•	
Total events	52		65					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 2.29 (P = 1	0.02)						
1.1.2 Diagnostic and	Statistical Ma	nual of N	lental Di	sorder	s (DSM-III	I)		
Lipsey 1984	5	17	8	22	5.1%	0.81 [0.32, 2.03]	· · · · · · · · · · · · · · · · · · ·	
Subtotal (95% CI)		17		22	5.1%	0.81 [0.32, 2.03]		
Total events	5		8					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.45 (P = 1	0.65)						
1.1.3 Montgomery-Å	sberg Depres	sion Rati	ing Scale	(MADI	RS)			
Ponzio 2001	82	112	97	117	22.1%	0.88 [0.77, 1.01]		
Murray 2002	7	62	4	61	3.4%	1.72 [0.53, 5.58]	· · · · · · · · · · · · · · · · · · ·	
Subtotal (95% CI)		174		178	25.6%	0.98 [0.59, 1.60]		
Total events	89		101					
Heterogeneity: Tau ² =	0.07; Chi ² = 1	.39, df =	1 (P = 0.2)	24); 12 =	28%			
Test for overall effect:	Z = 0.10 (P = 0).92)						
1.1.4 Hamilton Depre	ssion Rating	Scale (HI	ORS)					
Yang 2002	33	64	53	57	18.9%	0.55 [0.43, 0.71]		
Wang 2005	24	54	45	54	16.6%	0.53 [0.39, 0.74]		
Fruehwald 2003	8	28	6	26	5.2%	1.24 [0.50, 3.09]		
Andersen 1994	11	33	23	33	10.7%	0.48 [0.28, 0.81]		
Subtotal (95% CI)		179		170	51.4%	0.56 [0.46, 0.68]	◆	
Total events	76		127					
Heterogeneity: Tau ² =	0.01; Chi ² = 3	.36, df =	3 (P = 0.3	34); ² =	11%			
Test for overall effect:	Z= 5.72 (P < 1	0.00001)						
Total (95% CI)		520		505	100.0%	0.70 [0.55, 0.88]	•	
Total events	222		301					
Heterogeneity: Tau ² =	0.06; Chi ² = 2	1.68, df =	7 (P = 0	.003); F	² = 68%		0.2 0.5 1 2 5	
Test for overall effect:			287				Favours Pharmacotherapy Favours Placebo	
Test for subgroup diff	erences: Chi ²	= 5.51. d	f = 3 (P =	0.14)	² = 45.6%	6	Favours Filannacounerapy Favours Flacebo	

Figure. Effect of pharmacotherapy versus placebo on depression at the end of treatment, grouped by method used to determine depression.