Bijlage Evidence tabellen en GRADE profielen

Evidence tabellen en GRADE profielen behorende bij de uitgangsvragen die via de GRADE methodiek zijn uitgewerkt.

Onderzoeksvraag 1: niet-medicamenteuze behandeling

Wat is het effect van acupunctuur op hik bij patiënten in de palliatieve fase?
What is the effect of acupuncture on hiccups in patients in the palliative phase?

Patients	patients in the palliative phase with hiccups
Intervention	acupuncture
Comparator	pharmacological treatment, other non-pharmacological treatment for hiccups, sham-acupuncture, no treatment
Outcome	critical: hiccups (NRS, VAS), hiccup frequency, quality of life, sleep quality, patient satisfaction important: depression

Evidence tables

Systematic reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Cheon 2014	• Design: systematic review • Funding: supported by the National Research Foundation of Korea (NRF) Grant funded by the Korean government (Ministry of Science, ICT & Future Planning) (no. 2013R1A6A6029251) and a Grant from the National R & D Program for Cancer Control, Ministry for Health & Welfare, Republic of Korea (1020330); CoI: none • Search date: Mar 2013 • Databases: PubMed, Embase, CENTRAL,	• Eligibility criteria: cancer patients; reporting of clinical symptom improvement • Exclusion: studies reporting laboratory findings only	Pharmacopuncture	CRITICAL OUTCOMES • Hiccup (NRS, VAS): response rate ○ Sui 2009: 76% vs. 36.4%, p<0.05 ○ Xia 2000: 93.8% vs. 68.8%, p>0.05 • Hiccup frequency: not reported separately • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Depression: not reported	Level of evidence: high risk of bias • No language restriction • Selection and quality appraisal in duplicate, unclear for data extraction • Two relevant RCTs: Sui 2009, Xia 2000

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	CINAHL, CNKI, related Korean databases, trial registries • Study designs: RCTs • N included studies: N=22, of which 2 RCTs with hiccup patients				
Choi 2012	• Design: systematic review + meta-analysis • Funding: supported by Korea Institute of Oriental Medicine (C12080 and K11111); CoI: none • Search date: Jul 2011 • Databases: Medline, AMED, Embase, CINAHL, PsycINFO, Cochrane Library, CNKI, related Korean databases • Study designs: RCTs and quasi-RCTs • N included studies: N=5	• Eligibility criteria: patients with acute, persistent or intractable hiccups resulting from cancer	Acupuncture	CRITICAL OUTCOMES • Hiccup (NRS, VAS): response rate ○ Acupuncture vs. oral drug therapy (1 study, 62 patients): RR 1.36 (95%CI 1.03-1.79; p=0.03) ○ Acupuncture vs. intramuscular injection (3 studies, 162 patients): RR 1.87 (95%CI 1.26-2.78; p=0.002; I^2 37%) ○ Acupuncture + intramuscular injection vs. intramuscular injection (1 study, 72 patients): RR 2.39 (95%CI 1.30-4.34; p=0.005) ○ Acupuncture vs. intramuscular injection + self-care (1 study, 36 patients): RR 1.05 (95%CI 0.78-1.41; NS) • Hiccup frequency: ○ Acupuncture vs. oral drug therapy (1 study, 62 patients): hiccup-free time 4.4h vs. 11.8h, p<0.01 • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Depression: not reported	Level of evidence: high risk of bias • Languages: Korean, Chinese, English • Data extraction in duplicate, unclear for selection and quality appraisal • Included studies: Liu 2007, Chen 2006, Wang 2006, Luo 2007, Chen 2007
Hu 2015	• Design: systematic review + meta-analysis • Funding: not reported; CoI: none • Search date: Oct 2013 • Databases: Pubmed, AMED, Cochrane Library, CINAHL, PsycINFO,	• Eligibility criteria: patients with any condition	Acupuncture to GV 26	No separate results reported	Level of evidence: high risk of bias • Languages: English, Chinese • Duplicate quality appraisal, unclear for selection and data extraction • 1 included relevant RCT: Tian 2012 (abstract)

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	ScienceDirect, CNKI, VIP, Wanfan • Study designs: RCTs • N included studies: N=15, of which 1 RCT with hiccup patients				
Moretto 2013	• Design: systematic review • Funding: not reported; CoI: none • Search date: Nov 2012 • Databases: CENTRAL, Cochrane Library, DARE, Medline, Embase, CINAHL, PsycINFO, SIGLE • Study designs: RCTs, CCTs • N included studies: N=4	• Eligibility criteria: adults (over 18 years old) who had been diagnosed with persistent or intractable hiccup (i.e. hiccup episode lasting more than 48 hours) • Exclusion: acute hiccups	Acupuncture	CRITICAL OUTCOMES • Hiccup (NRS, VAS): not reported separately • Hiccup frequency: ○ Bao 2003: total cure rate 88.9% vs. 65%, p<0.05 ○ Han 2006: cure rate 100% vs. 30%, p<0.05 ○ Jiang 2002: total cure rate 90% vs. 70%, NS ○ Wang 2011: cure rate 77.5% vs. 50%, p<0.01 • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Depression: not reported	Level of evidence: high risk of bias • No language restriction • Duplicate review process • No meta-analysis performed due to methodological differences • Included studies: Bao 2003, Han 2006, Jiang 2002, Wang 2011
Yue 2017	• Design: systematic review + meta-analysis • Funding: supported by the Foundation of Heilongjiang University of Chinese Medicine (grant no. 2012RCQ64 and 2012RCL01) and the Foundation of Graduate Innovative Plan of Heilongjiang Province (grant no. YJSCX2012-357HLJ); CoI: none • Search date: Jun 2015 • Databases: Medline, Embase, CENTRAL, CINAHL, and four Chinese medical databases	• Eligibility criteria: patients suffering from hiccups following stroke • Exclusion: hiccups associated with cancer or other unclear mechanisms	Acupuncture	CRITICAL OUTCOMES • Hiccup (NRS, VAS): not reported separately • Hiccup frequency: cessation of hiccups within specified time period ○ Acupuncture + drug vs. drug alone (3 studies, 136 patients): RR 1.59 (95%CI 1.16-2.19; p=0.004) ○ Acupuncture vs. drug (2 studies, 123 patients): RR 1.40 (95%CI 0.79-2.47; p=0.24; I^2 65%) • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Depression: not reported	Level of evidence: high risk of bias • No language restriction • Duplicate review process • Included studies: Jiang 2010, Wei 2014, Yan 2012, Zhang 2006, Zong 2009

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Study designs: RCTs • N included studies: N=5				
Wu 2015	• Design: review of reviews • Funding: funded by Hospital Authority of Hong Kong (Reference number: 8110016609); CoI: none • Search date: Jul 2014 • Databases: Medline, Embase, CDSR, DARE, Chinese Biomedical Databases, Wan Fang Digital Journals and Taiwan Periodical Literature Databases • Study designs: SR • N included reviews: N=23, of which 2 on hiccup	• Eligibility criteria: patients with a diagnosis of any type of cancer who have received acupuncture and related therapies for supportive or palliative care	Acupuncture and related therapies	See above	Level of evidence: high risk of bias • Review process in duplicate • Unclear language restriction • Included reviews: Choi 2012, Cheon 2014

Primary studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Hongliang 2006	• Design: RCT • Funding: not reported; CoI: not reported • Setting: 2 university centres, China • Sample size: N=80 • Duration: Mar 2000 – Dec 2004	• Eligibility criteria: patients with hiccup due to stroke • *A priori* patient characteristics: ○ Mean age: 34-85y vs. 32-79y ○ Female: 40% vs. 45%	Acupuncture (30 min needle retention) and cupping for 3d (N=40) vs. Ritaline 20 mg IM once daily for 3d (N=40)	CRITICAL OUTCOMES • Hiccup (NRS, VAS): not reported separately • Hiccup frequency: ○ Total effective rate (cured, markedly effective or improved): 92.5% vs. 72.5%, p=0.0009 • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Depression: not reported	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Unclear blinding, but unlikely for patients and personnel • Definitions of efficacy: ○ Cured: disappearance of hiccup and no relapse within 1 week

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
					○ Markedly effective: hiccup basically relieved, but relapse within 1 week ○ Improved: frequency and severity reduced, no obvious improvement of morbid condition ○ Failed: no amelioration of hiccup
Wang 2004	• Design: RCT • Funding: not reported; CoI: not reported • Setting: single centre, China • Sample size: N=114 • Duration: 1996-2003	• Eligibility criteria: cancer patients in middle or late stage, being treated with chemotherapy or radiotherapy, hiccups within 2-3 days • *A priori* patient characteristics: ○ Mean age: 39-81y vs. 44-79y ○ Female: 26/56 vs. 19/58	Acupuncture 1x/d (30-40 min needle retention) (N=56) vs. Routine Western medicine: paspertin and vit. B6 IV 1x/d (N=58)	CRITICAL OUTCOMES • Hiccup (NRS, VAS): not reported separately • Hiccup frequency: ○ Total effective rate (cured or effective): 87.5% vs. 32.8%, p<0.01 • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Depression: not reported	Level of evidence: unclear risk of bias • Unclear randomisation method and allocation concealment • Unclear blinding, but unlikely for patients and personnel • Definitions of efficacy: ○ Cured: hiccups stopped after treatment ○ Effective: frequency of hiccups decreased after treatment ○ Ineffective: no change after treatment
Zhang 2017	• Design: RCT • Funding: supported by Shanghai Municipal Commission of Health and Family Planning (ZJ 2016008); CoI: not reported • Setting: single centre, China • Sample size: N=100 • Duration: 2 weeks	• Eligibility criteria: patients aged 30-75y with hiccup with onset of more than 3 days • Excluded: glaucoma, mental disorder, acute cerebral hemorrhage, patients in gestation period or lactating women, patients participating in other pharmaceutical studies, patients with heart, liver or kidney failure, patients being allergic to the drugs used in this study • *A priori* patient characteristics: ○ Mean age: 57.33 vs. 61.18y	Scalp acupuncture (1h needle retention) combined with herb decoction group (N=50) vs. Western medicine: intramuscular injection with 10 mg of anisodamine (N=50)	CRITICAL OUTCOMES • Hiccup (NRS, VAS): not reported separately • Hiccup frequency: ○ Total cure rate: 54% vs. 32%, p<0.05 ○ Total effective rate (cured, markedly effective or effective): 84% vs. 66%, p<0.05 • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Depression: not reported	Level of evidence: unclear risk of bias • Divided into treatment group and control group according to the visiting sequence by adopting the random number table method • Unclear allocation concealment • Unclear blinding, but unlikely for patients and personnel • Definitions of efficacy: ○ Cured: the symptoms disappeared in the

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
		○ Female: 42% vs. 54%			process of one course of treatment, without relapse during the follow-up visit for two weeks ○ Markedly effective: most symptoms disappeared in the one course of treatment, the interval of hiccup was obviously prolonged, and the times of hiccup reduced by more than 50% ○ Effective: the symptoms were improved slightly in the one course of treatment, and the times of hiccup reduced by 30% ○ Ineffective: the symptoms were not improved or did aggravate in the one course of treatment

Abbreviations: 95%CI: 95% confidence interval; CCT: controlled clinical trial; CoI: conflict of interest; NRS: numeric rating scale; NS: not significant; RCT: randomised controlled trial; RR: relative risk; VAS: visual analogue scale.

GRADE profiles

Pharmacopuncture

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pharmaco-puncture	Control	Relative (95%CI)	Absolute		
Hiccup: response rate												
2	RCT	Very serious[1]	Serious[2]	No serious indirectness	Serious[2]	None	41	38	-	○ Sui 2009: 76% vs. 36.4%, p<0.05 ○ Xia 2000: 93.8% vs.	VERY LOW	CRITICAL

										68.8%, p>0.05		
Hiccup frequency												
0	No evidence from RCTs											
Quality of life												
0	No evidence from RCTs											
Sleep quality												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Depression												
0	No evidence from RCTs											

[1] High risk of bias: possible issues with randomization and allocation concealment, no blinding.

[2] Inconsistent results.

[3] Precision unclear, no CI reported.

Acupuncture vs. oral drug therapy

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Acupuncture**	**Perphenazine**	**Relative (95%CI)**	**Absolute**		
Hiccup: response rate												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	32	30	RR 1.36 (1.03-1.79)	-	VERY LOW	CRITICAL
Hiccup-free time												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	32	30	-	4.4h vs. 11.8h p<0.01	VERY LOW	CRITICAL
Quality of life												
0	No evidence from RCTs											
Sleep quality												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Depression												

0	No evidence from RCTs

[1] High risk of bias: unclear allocation concealment and blinding.

[2] CI includes a threshold of 1.25.

[3] Precision unclear, no CI reported.

Acupuncture vs. intramuscular drug therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Acupuncture**	**IM drug**	**Relative (95%CI)**	**Absolute**		
Hiccup: response rate												
3	RCT	Very serious[1]	No serious inconsitency	No serious indirectness	No serious imprecision	None	99	63	RR 1.87 (1.26-2.78)	-	LOW	CRITICAL
Hiccup frequency												
0	No evidence from RCTs											
Quality of life												
0	No evidence from RCTs											
Sleep quality												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Depression												
0	No evidence from RCTs											

[1] High risk of bias: possible issues with randomization, allocation concealment, blinding.

Acupuncture + intramuscular drug therapy vs. intramsucular drug therapy alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Acupuncture + IM Ritalin**	**IM Ritalin**	**Relative (95%CI)**	**Absolute**		
Hiccup: response rate												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	24	24	RR 2.39 (1.30-4.34)	-	LOW	CRITICAL
Hiccup frequency												
0	No evidence from RCTs											

Quality of life	
0	No evidence from RCTs
Sleep quality	
0	No evidence from RCTs
Patient satisfaction	
0	No evidence from RCTs
Depression	
0	No evidence from RCTs

[1] High risk of bias: possible issues with randomization, allocation concealment, blinding.

Electro-acupuncture vs. intramsucular drug therapy alone + self-care

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Electro-acupuncture**	**IM metoclopramide + self-care**	**Relative (95%CI)**	**Absolute**		
Hiccup: response rate												
1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	24	12	RR 1.05 (0.78-1.41)	-	VERY LOW	CRITICAL
Hiccup frequency												
0	No evidence from RCTs											
Quality of life												
0	No evidence from RCTs											
Sleep quality												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Depression												
0	No evidence from RCTs											

[1] High risk of bias: possible issues with randomization, allocation concealment, blinding.

[2] CI includes a threshold of 1.25.

Acupuncture vs. intravenous drug therapy

Quality assessment	**No of patients**	**Effect**	**Quality**	**Importance**

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acupuncture	IV metoclopramide + vit. B6	Relative (95%CI)	Absolute		
Hiccup: total effective rate												
1	RCT	Very serious[1]	No serious inconsitency	No serious indirectness	Serious[2]	None	56	58	-	87.5% vs. 32.8% p<0.01	VERY LOW	CRITICAL
Hiccup frequency												
0	No evidence from RCTs											
Quality of life												
0	No evidence from RCTs											
Sleep quality												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Depression												
0	No evidence from RCTs											

[1] High risk of bias: possible issues with randomization, allocation concealment, blinding.

[2] Precision unclear, no CI reported.

Acupuncture in stroke patients

Acupuncture + drug vs. drug alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Acupuncture + drug**	**Drug alone**	**Relative (95%CI)**	**Absolute**		
Hiccup: cessation												
3	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	70	66	RR 1.59 (1.16-2.19)	-	LOW	CRITICAL
Hiccup frequency												
0	No evidence from RCTs											
Quality of life												
0	No evidence from RCTs											
Sleep quality												
0	No evidence from RCTs											

Patient satisfaction	
0	No evidence from RCTs
Depression	
0	No evidence from RCTs

[1] High risk of bias: possible issues with allocation concealment and blinding.

[2] CI includes a threshold of 1.25.

Acupuncture vs. drug therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Acupuncture**	**Drug therapy**	**Relative (95%CI)**	**Absolute**		
Hiccup: cessation												
2	RCT	Serious[1]	Serious[2]	No serious indirectness	Serious[3]	None	62	61	RR 1.40 (0.79-2.47)	-	VERY LOW	CRITICAL
Hiccup frequency												
0	No evidence from RCTs											
Quality of life												
0	No evidence from RCTs											
Sleep quality												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Depression												
0	No evidence from RCTs											

[1] High risk of bias: possible issues with allocation concealment and blinding.

[2] Inconsistent results.

[3] CI includes a threshold of 1.25.

Acupuncture + cupping vs. drug therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Acupuncture + cupping**	**IM Ritaline**	**Relative (95%CI)**	**Absolute**		
Hiccup: total effective rate												

1	RCT	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	40	40	-	92.5% vs. 72.5% p=0.0009	VERY LOW	CRITICAL
Hiccup frequency												
0	No evidence from RCTs											
Quality of life												
0	No evidence from RCTs											
Sleep quality												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Depression												
0	No evidence from RCTs											

[1] High risk of bias: possible issues with randomization, allocation concealment, and blinding.

[2] Precision unclear, no CI reported.

Acupuncture in patients with other conditions

Acupuncture vs. intramuscular drug therapy

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Acupuncture**	**IM Anisodamine**	**Relative (95%CI)**	**Absolute**		
Hiccup: total cure rate												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	50	50	-	54% vs. 32% p<0.5	VERY LOW	CRITICAL
Hiccup: total effective rate												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	50	50	-	84% vs. 66% p<0.5	VERY LOW	CRITICAL
Hiccup frequency												
0	No evidence from RCTs											
Quality of life												
0	No evidence from RCTs											
Sleep quality												

0	No evidence from RCTs
Patient satisfaction	
0	No evidence from RCTs
Depression	
0	No evidence from RCTs

[1] High risk of bias: possible issues with allocation concealment and blinding.

[2] Precision unclear, no CI reported.

References

1 Cheon S, Zhang X, Lee IS, Cho SH, Chae Y, Lee H. Pharmacopuncture for cancer care: A systematic review. Evidence-based Complementary and Alternative Medicine. 2014;2014.

2 Choi TY, Lee MS, Ernst E. Acupuncture for cancer patients suffering from hiccups: a systematic review and meta-analysis. Complement Ther Med. 2012;20(6):447-55.

3 Hongliang X, Xuemei C, Shizhao H, Chaofeng L. Acupuncture and cupping for treatment of hiccup in cases of cerebrovascular accident. J Tradit Chin Med. 2006;26(3):175-6.

4 Hu XY, Trevelyan E, Chai QY, Wang CC, Fei YT, Liu JP, et al. Effectiveness and safety of using acupoint Shui Gou (GV 26): A systematic review and meta-analysis of randomized controlled trials. Acupuncture and Related Therapies. 2015;3(1):1-10.

5 Moretto EN, Wee B, Wiffen PJ, Murchison AG. Interventions for treating persistent and intractable hiccups in adults. Cochrane Database Syst Rev. 2013(1):CD008768.

6 Wang F, Gao Q-Q. Treatment of intractable hiccup with acupuncture in 56 cancer patients. J acu tuina sci. 2004; 2(5):28.

7 Wu X, Chung VC, Hui EP, Ziea ET, Ng BF, Ho RS, et al. Effectiveness of acupuncture and related therapies for palliative care of cancer: overview of systematic reviews. Sci. 2015;5:16776.

8 Yue J, Liu M, Li J, Wang Y, Hung ES, Tong X, et al. Acupuncture for the treatment of hiccups following stroke: a systematic review and meta-analysis. Acupunct Med. 2017;35(1):2-8.

9 Zhang J-F, Wu Y-C, Fan Y-Z, Li S-S, Huang C-F. Acupuncture combined with herb decoction for intractable hiccup. World journal of acupuncture - moxibustion. 2017; 27(3):63-8.

Onderzoeksvraag 2: medicamenteuze behandeling
Wat is het effect van medicamenteuze behandeling op hik bij patiënten in de palliatieve fase?
What is the effect of pharmacological treatment on hiccups in patients in the palliative phase?

Patients	patients in the palliative phase with hiccups
Intervention	pharmacological treatment
Comparator	other pharmacological treatment, placebo, no treatment
Outcome	critical: hiccups (NRS, VAS), hiccup frequency, quality of life, sleep quality, patient satisfaction important: depression

Evidence tables

Systematic reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Adam 2020	• Design: systematic review • Funding: not reported; CoI: none • Search date: Mar 2019 • Databases: Medline, Embase, Cochrane Library, CINAHL, hand searching • Study designs: all • N included studies: N=4, of which 1 RCT (30 stroke patients)	• Eligibility criteria: people aged 18+ with life-threatening illness, hiccups of any etiology and any duration	Baclofen	CRITICAL OUTCOMES • Hiccup (NRS, VAS): not reported • Hiccup frequency: cessation of hiccups ○ RR=7.00; 95%CI 1.91-25.62; p=0.003 • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Depression: not reported	Level of evidence: unclear risk of bias • English literature only • Unclear if duplicate selection or quality appraisal • Data extraction by one researcher • 1 included RCT: Zhang 2014
Calsina-Berna 2012	• Design: systematic review • Funding: not reported; CoI: none • Search date: Jun 2011 • Databases: Medline, Scopus • Study designs: all • N included studies: N=32, of which 0 RCTs or CCTs	• Eligibility criteria: cancer patients	All interventions	CRITICAL OUTCOMES • Hiccup (NRS, VAS): not reported • Hiccup frequency: not reported • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Depression: not reported	Level of evidence: - • Languages: English, French, Spanish • Duplicate selection and critical appraisal, unclear for data extraction • Quality appraisal using levels of evidence
Moretto 2013	• Design: systematic review • Funding: not reported; CoI: none • Search date: Nov 2012 • Databases: CENTRAL, Cochrane Library, DARE,	• Eligibility criteria: adults (over 18 years old) who had been diagnosed with persistent or intractable hiccup (i.e. hiccup episode lasting more than 48 hours)	All interventions	CRITICAL OUTCOMES • Hiccup (NRS, VAS): not reported • Hiccup frequency: not reported • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported	Level of evidence: - • No language restriction • Duplicate review process

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Medline, Embase, CINAHL, PsycINFO, SIGLE • Study designs: RCTs, CCTs • N included studies: N=0	• Exclusion: acute hiccups		IMPORTANT OUTCOMES • Depression: not reported	• No studies included that evaluated pharmaceutical interventions
Steger 2015	• Design: systematic review • Funding: Zürich Center for Integrated Human Physiology; CoI: one author with CoI • Search date: Jun 2015 • Databases: PubMed, Embase, Cochrane Library • Study designs: all • N included studies: N=15, of which 2 RCTs	• Eligibility criteria: persistent and intractable hiccups in adults	Pharmacological treatment	CRITICAL OUTCOMES • Hiccup (NRS, VAS): not reported • Hiccup frequency: o Zhang 2014: cessation of hiccups RR=7.00; 95%CI 1.91-25.62; p=0.003 o Wang 2014: overall efficacy RR=2.8; 95%CI 1.1-6.9; p=0.03; cessation 12% vs. 0% (RR=5.00; 95%CI 0.26-97.00; p=0.29) • Quality of life: not reported • Sleep quality: not reported • Patient satisfaction: not reported IMPORTANT OUTCOMES • Depression: not reported	Level of evidence: high risk of bias • Languages: English, German • Unclear if review process in duplicate • 2 included RCTs: Zhang 2014 (baclofen), Wang 2014 (metoclopramide) • Quality appraisal using levels of evidence

Abbreviations: 95%CI: 95% confidence interval; CCT: controlled clinical trial; CoI: conflict of interest; NRS: numeric rating scale; RCT: randomised controlled trial; RR: relative risk; VAS: visual analogue scale.

GRADE profiles

Baclofen

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baclofen	Placebo	Relative (95%CI)	Absolute		
Hiccup: cessation												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	15	15	RR 7.00 1.91-25.62	-	MODERATE	CRITICAL
Hiccup frequency												
0	No evidence from RCTs											
Quality of life												
0	No evidence from RCTs											
Sleep quality												
0	No evidence from RCTs											

Patient satisfaction	
0	No evidence from RCTs
Depression	
0	No evidence from RCTs

[1] Unclear risk of bias: unclear blinding.

Metoclopramide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Metoclopramide**	**Placebo**	**Relative (95%CI)**	**Absolute**		
Hiccup: cessation												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	17	17	RR 5.00 (0.26-97.00)	-	VERY LOW	CRITICAL
Hiccup: overall efficacy												
1	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[3]	None	17	17	RR 2.8 (1.1-6.9)	-	LOW	CRITICAL
Hiccup frequency												
0	No evidence from RCTs											
Quality of life												
0	No evidence from RCTs											
Sleep quality												
0	No evidence from RCTs											
Patient satisfaction												
0	No evidence from RCTs											
Depression												
0	No evidence from RCTs											

[1] High risk of bias: 2/36 patients not included in analysis.

[2] CI includes 0.75 and 1.25.

[3] CI includes 1.25.

References

1 Adam E. A Systematic Review of the Effectiveness of Oral Baclofen in the Management of Hiccups in Adult Palliative Care Patients. J Pain Pall Care Pharmacother. 2020;34(1):43-54.

2 Calsina-Berna A, Garcia-Gomez G, Gonzalez-Barboteo J, Porta-Sales J. Treatment of chronic hiccups in cancer patients: a systematic review. J Palliat Med. 2012;15(10):1142-50.
3 Moretto EN, Wee B, Wiffen PJ, Murchison AG. Interventions for treating persistent and intractable hiccups in adults. Cochrane Database Syst Rev. 2013(1):CD008768.
4 Steger M, Schneemann M, Fox M. Systemic review: the pathogenesis and pharmacological treatment of hiccups. Aliment Pharmacol Ther. 2015;42(9):1037-50.
5 Wang T, Wang D. Metoclopramide for patients with intractable hiccups: a multicentre, randomised, controlled pilot study. Intern Med J. 2014;44(12a):1205-9.
6 Zhang C, Zhang R, Zhang S, Xu M, Zhang S. Baclofen for stroke patients with persistent hiccups: a randomized, double-blind, placebo-controlled trial. Trials. 2014;15:295.