

NHMRC Evidence Hierarchy	Palliative	Type of Study	Author	Year	# of pts	Underlying condition	Medication	Medication details	Effect	Adverse Effect
II	No	Randomized Controlled Trial	Ramirez FC et al[12]	1992	4	Idiopathic hiccups Exclusion: organic GI disease	Baclofen	Baclofen 5mg TDS for 3 days, then 10mg TDS for 3 days, tapering to zero for 4 days	Baclofen had statistically significant improvement in hiccups than placebo in terms of both cessation and subjective assessment.	Not mentioned
II	No	Randomized Controlled Trial	Zhang C et al[13]	2014	30	Stroke patients	Baclofen	Baclofen 10mg TDS 5 days	Baclofen had statistically significant higher number of patients who finished hiccups than placebo group. The efficacy was also higher. No mention of recurrence.	One case each of mild transient drowsiness and dizziness
II	No	Randomized Controlled Trial	Wang T et al[14]	2014	36	17 unspecified cancer, 14 stroke, 5 cerebral tumors	Metoclopramide	Metoclopramide 10mg TDS 15Days	2 patients (out of 17) showed complete cessation of the hiccups with metoclopramide. Subjective improvement was shown in 9 patients. Systematic review by Steger M et al (2015) indicates that result of this study was questionable based on low number of complete cessation and subjective assessment.	Mood change, dizziness, fatigue, constipation and vertigo

Appendix 1: Randomized Controlled Trials

NHMRC Evidence Hierarchy	Palliative	Type of Study	Author	Year	# of pts	Underlying condition	Medication	Medication details	Effect	Adverse Effect
IV	Yes & No	Case Reports	Friedgood CE et al[19]	1955	3	Case 1: Rectal Carcinoma	Chlorpromazine	Chlorpromazine 50mg IV	Hiccups ceased 3 minutes after administration of medication	Not mentioned
						Case 2: prostatectomy for BPH	Chlorpromazine	Chlorpromazine 25mg IV	2 weeks of attempt of various method, including IV barbiturates where not helpful. Hiccups ceased after a sleep after medication administration.	Not mentioned
						Case 3: Posterior wall infarct	Chlorpromazine	Chlorpromazine 50mg IV	On the fourth day, chlorpromazine 50mg IV was infused. Patient hiccups disappeared immediately.	Not mentioned
						Case 4: idiopathic hiccups	Chlorpromazine	Chlorpromazine 50mg IV	Hiccups stopped immediately after chlorpromazine IV infusion. 25mg Chlorpromazine tablets TDS were given for two months.	Skin rash
II	No	Randomized Controlled Trial	Wang T et al[14]	2014	36	17 unspecified cancer, 14 stroke, 5 cerebral tumors	Metoclopramide	Metoclopramide 10mg TDS 15Days	2 patients (out of 17) showed complete cessation of the hiccups with metoclopramide. Subjective improvement was shown in 9 patients. Systematic review by Steger M et al (2015) indicates that result of this study was questionable based on low number of complete cessation and subjective assessment.	Mood change, dizziness, fatigue, constipation and vertigo
IV	Yes	Case report	Turkyilmaz A et al[21]	2008	1	Esophageal adenocarcinoma with distal esophageal stricture and liver metastasis	Baclofen	Baclofen 5mg PO Q6h (improved next day) continued for next month, and gradually ceased over the next month	Failed trial of oral metoclopramide (40mg daily for 3 days) and chlorpromazine (50mg daily for 2 days) subsequently. Yet, hiccups were improved 1 day after baclofen initiation. No hiccups recurrence over the next few months	Not mentioned
IV	Yes	Case report	Walker et al[22]	1998	2	Case1: Prostate with metastasis to bone. Unknown cause of hiccups	Baclofen	Baclofen 10mg (TDS)	Trial of metoclopramide, haloperidol showed minimal improvement. Baclofen showed improvement the next day. Patient died of pneumonia on day 50 after admitted to PCU	Not mentioned
						Case3. Metastatic gastric cancer	Baclofen	Baclofen 10mg PO BD	Baclofen showed effect on first day of treatment. Ceased on day 3 and no recurrence observed	No adverse effect
IV	Yes	Case report	Hernandez JL et al[23]	2004	1	Metastatic gastric neoplasm (CT scan reveals metastatic lymphadenopathy over left diaphragm)	Baclofen and Gabapentin	Baclofen 15mg TDS and Gabapentin 400mg daily	Attempts to control hiccups by omeprazole, chlorpromazine or baclofen were not successful. Increased baclofen dosage and addition of gabapentin ceased hiccups in a day. Recurrence in a week later, and gabapentin was increased. Hiccups resolved in 2 days without recurrence for next 2 months	Not mentioned
IV	Yes	Case report	Rizzo C et al[24]	2014	1	Multiple myeloma, Plasma cell leukemia, asthma, GORD, Esophagitis	Baclofen and olanzapine	Baclofen 10mg PO TDS and olanzapine 7.5mg PO Nocte	Started with Baclofen 10mg BD and showed significant improvement within 24hr. Patient tolerate oral intake after 48hr. Further improvement with olanzapine. No further mention in regards to recurrence or ceasing medicine.	Not mentioned
IV	Yes	Case report	Menon M[25]	2012	1	60yo non-small cell cancer of lung with widespread mets: CXR showing irritation of phrenic nerve and diaphragm on right side	Gabapentin	Gabapentin 100mg	Symptoms resolved dramatically. Hiccup free for 1 month with complete resolution of hiccups with gabapentin.	Not mentioned
IV	Yes	Retrospective Chart Review	Porzio G et al[26]	2010	43	43 Primary tumor patients: 42 non-CNS cancer and 1 CNS cancer	Gabapentin	32 patients Gabapentin 900mg/d and 9 patients Gabapentin 1200mg/d	2 patients registered worsening hiccups required midazolam for care of dying pathway. Remaining 41 patients responded well. No mention of recurrence.	2 patients with grade 2 sleepiness and a patient with grade 1 sleepiness

IV	Yes	Case report	Kaneishi et al[27]	2013	1	Gastric Cancer	Lidocaine (CSCI)	Lidocaine 480mg(24ml)/day continuous subcutaneous injection	Hiccups occurred few times per day on day three, and it completely disappeared on day five. Pt died of primary disease on day nine	Adverse effect monitored, and non-observed
IV	Yes	Case report	Neuhaus T et al[28]	2012	4	Case 2. Pancreatic cancer with lung mets, cholestasis, pruritis	Lidocaine and Baclofen	5ml of viscous lidocaine (2-3/day) combination with 20mg/day baclofen	Hiccups persisted for 3 months without improvement when patient was receiving baclofen and neuroleptic medications. Patient died of cancer progression..	Not mentioned
IV	Yes	Case report	Marechal R[29]	2003	1	Lung cancer with brain, bone, mediastium and liver mets. Endoscopy reveals peptic esophagitis and gastroparesis	Methylphenidate	Metoclopramide 10mg QID and Methylphenidate 5mg BD	Failed attempt of haloperidole and chlorpromazine. Patients report significant improvement after methylphenidate introduction and hiccup free after 3 days. Complete relief was noted for 6 weeks	Not mentioned
IV	Yes	Case report	Wilcock A et al[30]	1996	2	Case1: Carcinoma of Left Kidney and Pulmonary Metastasis	Midazolam	Midazolam 10mg IV (Abrupt stop) Midazolam 30mg/12 subcut overnight and 10mg/12hr subcut during day.	No success with trial of multiple drugs (chlorpromazine, Asilone, Metoclopramide, ranitidine, haloperidole, baclofen). IV Midazolam (10mg) showed immediate improvement. Midazolam 30mg/12 subcut overnight and 10mg/12hr subcut during day. Patient died 2 days later without further hiccups or distress	Not mentioned
						Case2: Disseminated prostate cancer	Midazolam	Midazolam 10mg IV (Immediate) Midazolam 120mg/24hr subcut	No success with trial of other drugs (metoclopramide, haloperidol). Refractory after 5mg IV Midazolam.	Increasingly sleepy
IV	Yes	Case report	Moro C et al[31]	2005	1	Colon cancer with liver metastases and gastric hypotonia	Midazolam	Subcut midazolam 60mg/day, morphine 30mg/day and chlorpromazine (unknown dose)	Failed trial of PPI, metoclopramide, haloperidole and chlorpromazine noted. Subcutaneous infusion of 15mg/day midazolam and morphine 20mg/day improved symptom for a day without sedation. Recurrence of hiccups on next day requires increasing the dose of midazolam to 60mg/day and morphine to 30mg/day and chlorpromazine.	Mild sedation, but awoken enough to talk. Not confused until last week.
IV	No	Case Report	Kockar C et al[32]	2009	2	Case1: grade B esophagitis	Omeprazole	Omeprazole 20mg BD PO and Sucralfate 1g QID	Hiccup was resolved after three days of the treatment. Helicobacter pylori infection was detected subsequently and treated with Clarithromycin 500mg/day and amoxicillin-clavulanic acid 2g/day. Hiccup was not repeated in 2 years	Not mentioned
						Case2: grade A esophagitis	Lansoprazole	Lansoprazole 30mg BD and Sucralfate 1g QID	Hiccup was resolved after five days of treatment. It was not repeated for 1 year.	Not mentioned
IV	Yes	Case report	Hernandes JL et al[18]	1999	2	Case 2: malignant peritoneal sarcoma and extensive metastatic disease in the liver	Nimodipine	IV Nimodipine 10mg/24hr	Failed attempt with baclofen and phenothiazine. IV nimodipine 10mg/24 showed complete relief for next 3 weeks	Not mentioned

Appendix 2: Management of peripheral causes of hiccups

NHMRC Evidence Hierarchy	Palliative	Type of Study	Author	Year	# of pts	Underlying condition	Medication	Medication details	Effect	Adverse Effect
II	No	Randomized Controlled Trial	Zhang C et al[13]	2014	30	Stroke patients	Baclofen	Baclofen 10mg TDS 5 days	Baclofen had statistically significant higher number of patients who finished hiccups than placebo group. The efficacy was also higher. No mention of recurrence.	One case each of mild transient drowsiness and dizziness
II	No	Randomized Controlled Trial	Wang T et al[14]	2014	36	17 unspecified cancer, 14 stroke, 5 cerebral tumors	Metoclopramide	Metoclopramide 10mg TDS 15Days	2 patients (out of 17) showed complete cessation of the hiccups with metoclopramide. Subjective improvement was shown in 9 patients. Systematic review by Steger M et al (2015) indicates that result of this study was questionable based on low number of complete cessation and subjective assessment.	Mood change, dizziness, fatigue, constipation and vertigo
IV	No	Case report	Hernandez JL et al[18]	1999	2	Case1: HIV patient with PML	Nimodipine	Nimodipine PO 30mg Q8h	No improvement with metoclopramide and baclofen. Nimodipine showed improvement within 24 hours and patient remained free of hiccups with maintenance of nimodipine	
IV	No	Case series	Boz C et al[34]	2001	10	Brainstem lesion	Baclofen	Baclofen 5BD and subsequent increase into 15-45mg TDS.	Not successful with metoclopramide, chlorpromazine, amitriptyline and carbamazepine as monotherapy or combination in 5 patients. Changed to baclofen showed better control. Other 5 patients started with baclofen, and hiccups improved dramatically within 12-72h. 6 patients had recurrence hiccups after discontinuation of baclofen (3-12 months).	Not mentioned
IV	No	Case series	Fodstad D et al[35]	1993	3	Case1: lesion on C3 to C7	Baclofen	Baclofen 40mg daily	Medical therapy and phrenic nerve block were not successful. Baclofen 40mg/day diminish hiccups after 1 week	Not mentioned
						Case2: cervical spine and cerebral aneurysm	Baclofen	Baclofen 40mg daily	Medical therapy and phrenic nerve stimulator was not successful. Treating cerebral aneurysm was not successful either. Baclofen 20mg reduced hiccup attacks whereas 40mg abolished the singultus. Hiccups free for 9 months	Not mentioned
IV	No	Case series	Moretti R et al[36]	1999	8	Brainstem lesion	Gabapentin	Gabapentin 400mg TDS for 3days, and 400mg/day for further 3 days.	Complete asymptomatic during second day of treatment.	No adverse effect
IV	No	Followup-case series	Moretti R et al[37]	2004	15	Brainstem lesion	Gabapentin	Gabapentin 400mg TDS for 3days, and 400mg/day for further 3 days.	Relief of hiccups was achieved promptly. 36 months followup showed no recurrence of intractable hiccups	No adverse effect
IV	No	Case report	Carlisi E et al[38]	2012	1	Post-AV malformation surgery: along with nerve palsies and esophagitis	Gabapentin	Gabapentin 400mg TDS	Failed trial of chlorpromazine or proton-pump inhibitor. Significant improvement after gabapentin. No recurrence after 12 months followup. No specific information regarding duration of gabapentin	Not mentioned
IV	Yes	Case report	Ives et al[39]	1985	1	Astrocytoma	Haloperidol	Intramuscular Haloperidol 1mg/12hr	Rapid action, but remission within 1hr	Not mentioned
IV	No	Case report	Baumann A et al [33]	2013	1	Brainstem compression	Baclofen	Baclofen 10mg TDS for 14 days	Failed trial of metoclopramide, chlorpromazine and haloperidol. Stat dose of baclofen 20mg was administered by nasogastric tube. Baclofen 10mg TDS were given for 14 days. Hiccup did not recur.	Not mentioned

Appendix 3: Management of central causes of hiccups

NHMRC Evidence Hierarchy	Palliative?	Type of Study	Author	Year	# of pts	Underlying condition	Surgery/Procedure	Details
IV	Yes	Case report	Arsanious D et al[40]	2016	1	esophageal dilation and/or phrenic or vagal fiber irritation	Ultrasound-guided phrenic or vagal nerve block	Medical therapy showed no relief. Left and right phrenic nerve block with bupivacaine and depomedrol showed complete resolution of hiccups and associated mediastinal pain.
IV	No	Followup-Case report	Sa YJ[41]	2014	1	Fall from height of 10m	2nd: cervical phrenic nerbe block under electromyography	Hiccups resolved for 3 months. Then, the patient developed hiccups bouts, which resolved with coke. No further hiccups for 12 months.
IV	No	Case report	Kim JJ et al[42]	2013	1	Fall from height of 10m	1st: Clipping of intrathoracic phrenic nerve	Hiccups resovlved well without post-op complication. However, persistent hiccups' recurred after 6 months
IV	No	Case report	Byun SH et al[43]	2012	1	No significant past medical history. Idiopathic	Positive Pressure Ventilation	Medical and procedural intervention failed. Propofol 2.0 mg/Kg, succinylcholine 70mg, air/oxygen 50% oxygen. Tital volume 650ml, 8 breath per minute, peak inspiratory pressure was 25cm H2O. No further epidosde of hiccups for 10 week.
IV	No	Case report	Schulz-Stubner S et al[44]	2011	1	Severe left basal ganglia and intraventricular bleed with hydrocephalus	Transcutaneous phrenic and vagal nerve stimulation	The left interscalene groove was stimulated at a frequency of 1Hz for 30s and then a brief tetanic stimulus was applied. Potential side effect of bradycardia and vomiting
IV	No	Case report	Payne BR et al[45]	2005	1	Posterior fossa stroke	Vagus nerve stimulation	Multiple medical and surgical therapies failed. Peripheral nerve stimulator lead was implanted to left vagus nerve. This was externalized for trail of stimulation. Rapid activation of device after a hiccup could prevent persistent hiccups..

Appendix 4: Potential procedures to treat intractable hiccups