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# TREATMENT APPROACHES FOR PERSISTENT AND INTRACTABLE HICCUPS: A SYSTEMATIC REVIEW AND RECOMMENDATIONS

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**Abstract**

**Background:**

Hiccups, involuntary contractions of the diaphragm, are commonly benign but can become distressing when persistent or intractable. While acute hiccups are self-limiting, lasting only a few minutes, persistent cases lasting days or months pose challenges in management.

**Objective**:

To evaluate existing treatment modalities for persistent and intractable hiccups and propose evidence-based recommendations.

**Methods**:

A systematic review was conducted to assess the efficacy of various treatments for persistent and intractable hiccups. Studies were included if they reported on interventions targeting hiccups and provided measurable outcomes. The search encompassed randomized controlled trials, observational studies, and case reports.

**Results**:

Treatment of 341 patients with persistent or intractable hiccups was reported in 15 published studies. Management was most effective when directed at the underlying condition. An empirical trial of anti-reflux therapy may be appropriate. If the underlying cause is not known or not treatable, then a range of pharmacological agents may provide benefit; however, a systematic review revealed no adequately powered, well-designed trials of treatment. Small randomized, placebo-controlled trials support the

use of baclofen and metoclopramide. The review identified a scarcity of adequately powered, well-designed trials on hiccup management. Empirical treatment targeting underlying causes, such as gastroesophageal reflux disease (GERD), was recommended if evident. Pharmacological interventions targeting dopaminergic and GABAergic receptors, such as baclofen and metoclopramide, showed promise in small randomized, placebo-controlled trials. Observational studies also suggested efficacy for Gabapentin and chlorpromazine, although associated side effects warrant caution.

**Conclusion**:

A treatment algorithm (Figure 3) is proposed based on available evidence, with baclofen as first-line therapy for persistent and intractable hiccups. Gabapentin may offer a safe and effective alternative, particularly for patients with central nervous system (CNS) involvement. However, long-term use of phenothiazines, including metoclopramide, is discouraged due to potential neurological and other adverse effects. Clinical decisions should align with recommendations from regulatory bodies and consider individual patient factors.

## INTRODUCTION

Hiccups are familiar to everyone but remain a poorly understood phenomenon caused by involuntary, repetitive contractions of the diaphragm and, in many cases, the intercostal muscles (Video S1). The medical term for this condition is ‘Singultus’, which can be translated from Latin as ‘to be caught in the act of sobbing’. The coordinated contraction of the inspiratory musculature leads to a rapid air intake within a few milliseconds, interrupted by the closure of the glottis. This results in the characteristic sound, the ‘hic’ in his cups, between 4 and 60 times a minute. In adults, it appears to serve no physiological purpose; however, the frequent observation of hiccups in utero during prenatal ultrasound examinations suggests that it may have a role in training inspiratory muscles in readiness for respiration after delivery(Devi).

### Epidemiology

The classification of hiccups is based on their duration.3 An acute attack lasts less than 48 h. ‘Persistent hiccups’ last more than two days. ‘Intractable hiccups’ are present if the attack lasts more than one month. The Guinness Book of Records documents the most prolonged period of continuous hiccupping at 69 years and nine months. At last, this attack was cured by prayers to St Jude... the patron saint of lost causes! Acute hiccups are a familiar experience that is very common in children but also experienced by adults. It is self-limiting and rarely requires pharmacological treatment because physical manoeuvres exist to foreshorten the attack (see below). The incidence and prevalence of persistent and intractable hiccups in the community have not been studied. A retrospective review of consecutive patients attending a general hospital identified 55 of 100 000 patients that received a primary diagnosis of hiccups.4 Hiccups are more common in diseases affecting the gastrointestinal or central nervous systems (CNSs). Up to 20% of patients with Parkinson’s disease and 10% with reflux symptoms complain of recurrent hiccups compared to approximately 3% of controls.5, 6 Overall, the prevalence of advanced cancer has been reported as 3.9–4.8%.7 However, in one case series, more than a quarter of patients with oesophageal carcinoma reported at least one attack of hiccups lasting more than 48 h. Irrespective of the underlying condition, when the situation is difficult to control, this impacts on patient’s quality of life and mood by interfering with eating, social interaction and sleep(Sardana and Sachdeva 2022).

### Pathophysiology

Hiccups are spontaneous myoclonia contractions of the diaphragm and, in many cases, the intercostal muscular truth. As first proposed by Bailey in 1943, it is widely accepted that hiccups are generated by a ‘reflex arc’ with afferent, central and efferent components (Figure 1).8 The afferent impulse is carried by the vagus nerve, phrenic nerves or sympathetic nerve fibres (thoracic outflow T6–T12). Areas of the CNS involved in the hiccup response appear to include the upper spinal cord (C3–C5), the brainstem in the medulla oblongata near the respiratory centre, the reticular formation and the

hypothalamus. Dopaminergic and gamma-amino-bu lyric-acid (GABA-ergic) neurotransmitters can modulate this central mechanism. The phrenic nerve carries the efferent response of the reflex to the diaphragm that has been observed to contract unilaterally or, less often, bilaterally. Activation of the accessory nerves leads to contraction also of the intercostal muscles. This stereotyped sequence of events is completed by reflex closure of the glottis by the recurrent laryngeal branch of the vagus nerve. Glottal closure is a vital protective reflex because patients with tra dichotomy hiccups lead to significant hyperventilation without it(García, Lertxundi et al. 2021).

**Causes of hiccups**

Any process affecting the proposed reflex arc's afferent, central or efferent components can trigger hiccups. The most common cause is stomach distension from a large meal or carbonated drinks. The reflex can also be triggered by hot chilli pepper, alcohol, smoking and other irritants to the gastrointestinal or pulmonary tracts. Hiccups can also be triggered by over-excitement or anxiety, especially if accompanied by over-breathing or air swallowing (aerophagia). Patients with persistent or intractable hiccups should be investigated to identify organic pathology. Over 100 possible associations have been described in the literature; however, many are based only on individual case reports. Table 1 provides an overview of pathology that has been reliably linked to this condition. Relatively common CNS causes of hiccups include cerebrovascular disease, brain tumours and intracranial injury(Shankar, Pillai et al. 2022)

I am presenting symptoms of severe neurological disease. Reflux oesophagitis and a large hiatus hernia are often cited as causes of persistent hiccups10; however, reflux can be the effect and cause of hiccups.11 Manometry and pH-impedance monitoring have shown that hiccups can inhibit normal oesophageal motility, reduce lower oesophageal sphincter pressure and alter the normal anatomy of the oesophagogastric junction, all of which favour gastro-oesophageal reflux (GERD; Fig ure 2). Cardiovascular diseases such as myocardial ischaemia, pericarditis and aortic aneurysm have been associated with persistent hiccups, as have nasal, pharyngeal and laryngeal conditions, including the presence of foreign bodies in the external auditory canal. Other causes linked to hiccups through effects on neural function include alterations to the electrolyte balance, uraemia and hyperglycaemia, plus a range of toxins and recreational drugs. Hiccups are also a recognized side effect of medications such as benzodiazepines, opiates and steroids. The problem can appear after surgery or endoscopy due to sedation, oro-pharyngeal intubation or enlargement of the stomach during the procedure. Psychogenic causes should not be overlooked in patients with anxiety disorders, acute stress or excitement. However, this should be considered a 'diagnosis of exclusion' in persistent hiccups, especially if repetitive diaphragmatic contractions persist during sleep(Katzka and Kahrilas 2020).

**Investigation**

Searching for the cause of hiccups can be challenging due to the long course of afferent and efferent nerves and the diffuse central processing of the 'reflex arc'. The medical and surgical history should explore possible triggers for hiccups and document the frequency and duration of the condition. A thorough list of prescribed and over-the-counter medications, alcohol, smoking and recreational drug intake should be taken. The physical survey should include the ears, nose, neck and throat, plus a full chest, abdominal and neurological examination. In addition to routine laboratory and imaging, computer tomography of the head, chest and abdomen is performed early to detect pathology along the course of the vagal and phrenic nerves. An upper gastrointestinal endoscopy is indicated. If no pathology is visualized, then an oesophageal manometry and a 24-h pH-impe dance reflux study should be considered, as GERD may be the most common trigger of hiccups.10 If neurological symptoms or signs are identified, Magnetic Resonance Imaging of the head and neck is the most sensitive method to identify CNS pathology, including the brainstem and cranial nerves(Kim, Lee et al. 2018).

**Therapy**

Whenever possible, the treatment of hiccups should be directed at the underlying cause of the condition. If no specific pathology has been identified or no definitive treatment is possible, then a wide range of physical (Table 2) and pharmacological treatments have been described for hiccups. The large number of medications proposed for this indication is a clear indication, first of the lack of knowledge concerning the underlying pathophysiology of this condition and, second, that no one approach is practical in most cases. Notwithstanding the above, recent years have seen new trials and case series enter the literature. Regulatory bodies have also published new recommendations concerning pharmacological agents for this indication(Ikitimur, Uysal et al. 2021).

AIMS

In light of new evidence, this article provides a systematic review documenting the efficacy and safety of empirical pharmacological treatment for persistent and intractable hiccups in adults. A brief overview of physical and nonpharmacological therapies is also provided(Kim, Lee et al. 2018)...

METHOD

A comprehensive search strategy was developed to identify relevant studies on hiccup therapy.

Available articles were identified using three electronic databases (Cochrane Library, Embase, PubMed). In addition, hand searching of the reference lists of relevant reviews and included studies was undertaken to identify further relevant publications. Inclusion criteria were any reports of ‘hiccup(s)’, ‘hiccough(s)’ or ‘Singultus' therapy written in English or German. The last search was run on 28 June 2015. The inclusion criteria were trials of adult patients treated with pharmacological therapy. The initial review revealed only two randomized, active treatment comparisons with placebo or standard care. Thus, the search was expanded to include therapy outcomes in case series and other treatment reports in patients without a control group. Case reports based on less than four patients are not detailed in the main table of results and are mentioned in the text only if the findings were considered to be of potential(Adam 2020)

"Hiccup Center" upper spinal cord (C3–C5), in the medulla oblongata near the respiratory

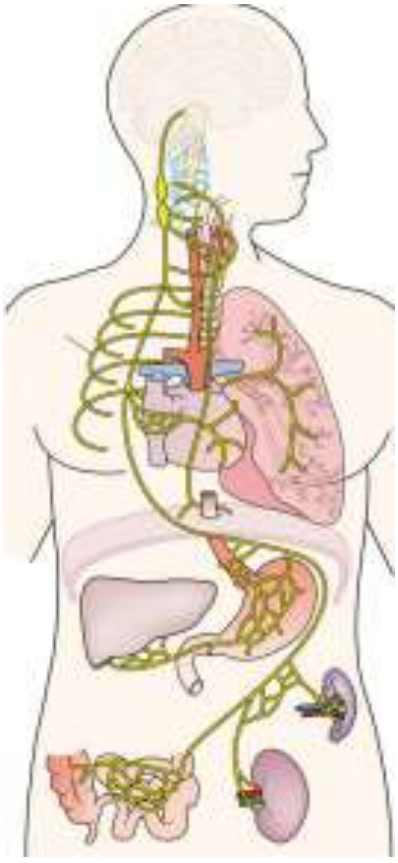


**Figure 1** | Anatomy of the hiccups reflux arc (after Bailey 1943). Pathology affecting the brain, diaphragm, thoracic or abdominal viscera can

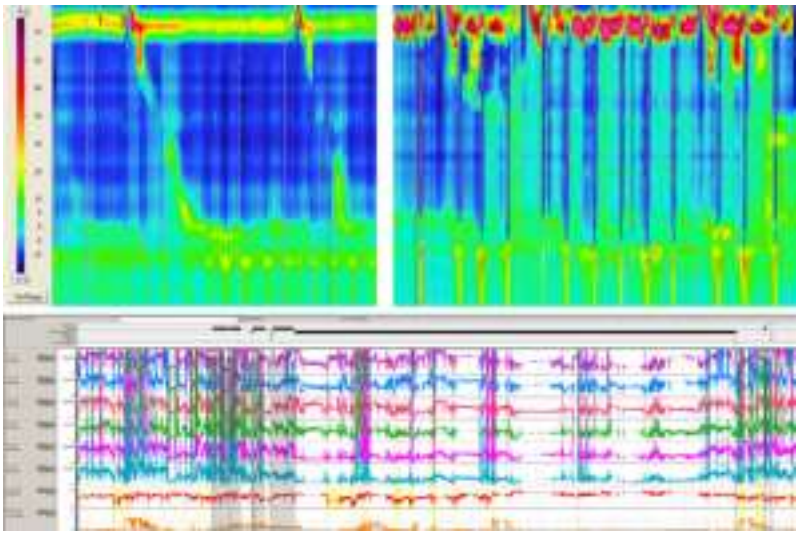
stimulate vagal or phrenic afferents to activate the diffuse 'hiccup centre' in the midbrain, brainstem and proximal cervical cord
**(Table 1)**. This triggers repetitive myoclonic contractions of the diaphragm and other respiratory muscles via the phrenic and the intercostal nerves (motor efferents coloured red). Immediately afterwards, activation of the recurrent laryngeal nerve (RLN) closes the glottis, producing the characteristic «hic» in hiccups. Publications were excluded if they did not report original data but were based on the same data as previous work, interviews and expert opinions in reviews. A comprehensive list of all agents with putative efficacy in hiccups is provided by the last reviewers.2, 8, 12, 13 Levels of evidence and recommendations are based on those proposed by the Oxford Center for Evidence-Based Medicine (cebm.net). ‘’

## RESULTS

### Description of included studies

Three hundred forty-one patients with persistent or intractable hiccups received empirical pharmacological therapy, as reported in 15 unique publications. The systematic analysis is summarised in Table 3. The quality of evidence for each pharmacological agent is documented in Table 4. Two small, well-designed, randomized controlled studies have been performed, one for metoclo pride (n = 36) and one for baclofen (n = 30). In addition, 13 case series (n = 4–50) were identified. Some were prospective, reporting on treatment effects in patients referred for investigation and treatment. Others were retrospective case note reviews. The standard of reporting was varied (detailed below). Several short reports from the 1970s and earlier were included for which complete information could not be obtained. This includes the two series from the 1950s that reported on the use of chlorpromazine.14, 15 We considered desire regarding this data; however, no other studies exist, and it seems very unlikely that this work will be repeated. The results are clinically relevant as neuroleptics remain the standard therapy in many institutions. On this basis, these results were included. Studies that reported on the effects of treating the underlying cause of hiccups were not included because, in these cases, there is no reason to consider that the mechanism of pharmacological action had specific effects on hiccups. This included a sizeable clinical case series by Cabane et al. on using proton pump inhibitors (PPI) in patients with GERD-related hiccups. This study identified upper digestive abnormalities in 146/183 (80%) patients with recurrent hiccups. Treatment of reflux and related digestive disorders in this group yielded 66% improvement in the subjective severity of hiccups, including complete cessation in one-third of patients.10 Note that these results should be interpreted with caution because of the lack of control group and the fact that reflux can be the effect as well as the cause of hiccups.11 Results from Petroianu et al. also studied the impact of PPI in the empirical management of hiccups; however, this study was included (Ehret, Le-Rademacher et al. 2022)
1040 Aliment Pharmacol Ther 2015; 4
Ischaemic/hammer **Patient characteristic analysis**
Persistent and intractable hiccups were defined by Kolodzik et al. in 1991.3 In earlier case series and some subsequent papers, the duration of hiccups was not always recorded. Case series that included patients with acute hiccups were excluded from this systematic review; however, it was impossible to verify that all patients included in all studies had more than 48 h continuous hiccups before treatment. We included studies that recruited patients that did not have hiccups all the time but had frequent episodes of hiccups over days, weeks or longer that required therapy. The causes of hiccups are varied, and it follows that the patients recruited to studies and case series were highly heterogeneous. Many studies limited recruitment to patients with hiccups related to conditions that reflected the speciality of the authors. General physicians and gas gastroenterologists reported treatment of hiccups related to gastrointestinal disorders. Neurologists said patients with hiccups related predominantly to cerebrovascular injury, brain tumours or multiple sclerosis. Paediatric populations were not included in this review. Several studies that reported the efficacy of second-line medications (e.g. anticonvulsants) limited recruitment to individuals that had not responded to other drugs, such as

chlorpromazine. Many papers did not specify any exclusion criteria. However, patients with renal insufficiency were excluded from studies of baclofen because sedation and other neurological side effects of this excreted drug are increased in this group.18 In other papers, patients with severe co-morbidity and psychiatric disorders were excluded due to concerns about drug interactions (Al-hajri, Ahmed et al. 2021).



Reflux
peristalsis
Figure 2 | Oesophageal function before and during an acute attack of hiccups in a patient with hiatus hernia and gastro-oesophageal reflux disease. High-resolution manometry demonstrates characteristic short contractions of the crural diaphragm during hiccups. Note suppression of peristalsis and lower oesophageal sphincter function. This patient had recurrent episodes of hiccups and responded to medical anti-reflux therapy. UES, upper oesophageal sphincter; LES, lower oesophageal sphincter; CD, crural diaphragm.

**Therapeutic intervention**

Several pharmacological agents are reported to have Effi cacy for the empirical treatment of persistent and intractable hiccups. The majority of these are directed at the dopaminergic and GABA-ergic receptors. The published reports all document efficacy for the substance tested. It is almost sure that this represents a positive write-up and publication bias (not formally tested). Two large case series from the 1950s document the efficacy of intravenous chlorpromazine for the cessation of persistent hiccups.14, 15 In current practice, this medication is given orally for maintenance therapy; however, within our search, the efficacy of this delivery route was not reported. Notwithstanding limited published evidence, oral chlorpromazine became the standard of care, and subsequent studies often used 'failure to respond to [oral] chlorpromazine' as the reason to attempt therapeutic trials of other pharmacological agents. It was never stated what proportion of patients with persistent or intractable hiccups failed to respond to 'standard care' with this neuroleptic medication.

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choice of medications was related to the speciality of the authors. General physicians and gastroenterology gists applied neuroleptics, metoclopramide or baclofen (one small case series reported efficacy for nifedipine). Neurologists applied baclofen or anticonvulsants (most often Gabapentin). As a result, the evidence that Gabapentin is effective for hiccups related to CNS disease is relatively strong, whereas it is limited for hiccups about gastrointestinal pathology. Several studies have documented the effect of acupuncture therapy in patients with hiccups and were summarised by a Cochrane review.19 Other nonpharma ecological treatments subjected to formal assessment include positive pressure ventilation, hypnosis and surgical procedures to disrupt or stimulate nerves involved

in the 'reflex arc' (see recent review2). All these nonpharmacological approaches may be practical, but high-quality data support none(Desanti-Siska, Fellows et al. 2021).

**Choice of outcome measures**

There are no validated questionnaires documenting the severity of persistent and intractable hiccups. All studies reported whether there was complete cessation after treatment. Many studies also reported a subjective reduction in 'hiccup frequency' and an increase in 'hiccup-free periods'. Sometimes, an arbitrary threshold was applied (e.g. '50% improvement)(Tariq, Das et al. 2021).

**Reporting of side effects**

Sedation and other neurological side effects (e.g. fatigue, sedation, dizziness) were not reported by all studies; however, these can be associated with all medications with efficacy in hiccups. When registered, the frequency of side effects was up to 50% for neuroleptic drugs, and this appeared to be more frequent for chlorpromazine15 and metoclopramide20 than for baclofen at standard doses21, 22 or gabapentin.7 Very little data was available for other medications(Amundson, Knight et al. 2022).

**Limitations of the data**

There are significant limitations to the evidence base supporting pharmacological treatment for persistent and intractable hiccups. This includes patient selection (inconsistently defined, heterogeneous), study design (often retrospective case series, often no control intervention) and reporting of pharmacological and other interventions. This precluded a formal meta-analysis. A systematic review of the data was performed.

## DISCUSSION

When possible, therapy for persistent hiccups should be directed at the underlying cause of the condition. This could be as simple as treating reflux disease with proton pump inhibitors or as complex as significant surgery to remove a neoplastic lesion from the brainstem. If no specific pathology has been identified or no definitive treatment is possible, then a range of empirical medical therapies have been described to treat hiccups. However, our literature search revealed only two randomized clinical trials and the bulk of 'evidence' for most pharmacological treatments of this condition is based on case series. In acute hiccups, physical manoeuvres are often effective (Table 2). Many of these 'remedies' have not been tested, and some appear to have been invented 'purely for the amusement of the patient's friends.23 The principle that links these manoeuvres is the attempt to interrupt or suppress the reflex arc (Figure 1) thought to maintain repetitive diaphragmatic contractions.8, 12 This is most often attempted by breath-holding, the Valsalva manoeuvre or rebreathing into a paper bag(Ikitimur, Uysal et al. 2021).

Recommendations for treatment of persistent and intractable hiccups. Levels of evidence are based on those proposed by the Oxford Centre for Evidence-Based Medicine (cebm.net). Pharmacological agents in the italic script are noted as alternatives to more established medications that have demonstrated a mechanism by which these manoeuvres improve hiccups, decreasing the frequency of hiccups as arterial pCO2 rises.9 This experimental evidence, backed up by the personal experience of the senior author, suggests that an effective method to interrupt hiccups is to hold one's breath during expiration (diaphragm relaxed, pCO2 high). Other techniques that can lead to the cessation of hiccups involve stimulation of the nose, ear or throat (e.g. ice cold drinks), eyeball pressure, carotid massage or self-induced vomiting. Techniques that 'push against the diaphragm by drawing up the legs to the chest (i.e. 'rolling into a ball') may also be helpful. Rectal massage and sexual stimulation have also been reported to help24 25; however, we recommend this kind of recommendation for carefully selected patients! A wide range of pharmacological treatments has been used to terminate persistent and intractable hiccups

It has been noted that some of the medications used to treat hiccups have also been implicated in their cause (e.g. benzodiazepines).26 Analogous to the effects of alcohol intake on arousal, low doses of these medications may lead to disinhibition of the 'hiccups reflex'. In contrast, high doses have a

general inhibitory effect and suppress repetitive contractions. In the absence of comparative studies, the choice of medication should consider any underlying cause, the patient's medical status and possible side effects. For example, in gastroenterological practice, reflux disease symptoms are common in patients with intermittent acute or persistent hiccups. In such cases, the senior author provides an initial trial of acid and reflux suppression (e.g. Omeprazole 20 mg b.d. with Gaviscon Liquid 10 ml after meals). Cabane et al. have shown that this empirical approach is safe, well tolerated
.

These medications are thought to act by dopamine blockade in the hypothalamus; however, it is uncertain whether these 'major sedatives' terminate hiccups through a general inhibitory effect or specific effects on particular neurotransmitters. The use of chlorpromazine is supported by two large case series (n = 50) published in the 1950s, shortly after these medications became available.14, 15 This became the standard of care, and subsequent case series often used' failure to respond to chlorpromazine' as the reason to attempt therapeutic trials of other pharmacological agents. Chlorpromazine was, until recently, recommended for use in persistent hiccups by the American Food and Drug Administration (FDA). This approval was withdrawn due to concerns regarding long-term neurological and other side effects. Be effective at controlling hiccups; however, their use is also limited by side effects such as dizziness, mood disturbance and sedation. Metoclopramide is a benzamide that shares a similar chemical structure to neuroleptic agents; however, it is less sedative and has essential effects on dopamine (D3 antagonist) and serotoninergic (5-HT4 agonist) receptors with both central antiemetic and peripheral prokinetic effects. The latter may be helpful in hiccups because promoting gastric emptying reduces both gastric distension and GERD. Reviewers support the use of metoclopramide, case reports and one recent randomized controlled trial.8, 12, 20 Wang and Wang randomized 36 patients with persistent hiccups to metoclopramide or placebo and demonstrated a benefit of active medication in terms of 'termination or improvement' of hiccups (odds ratio for combined endpoint 2.75; CI 95% 1.09–6.94, P = 0.03).9 Acute side effects were present but rarely severe and did not prevent treatment. More concern to patients with intractable hiccups is the risk of long-term dyskinesia when metoclopramide is given as maintenance therapy over a more extended period.29 Domperidone is a dopamine antagonist that shares many peripheral actions of metoclopramide but does not cross the blood-brain barrier and has rarely been associated with neurological side effects. On this basis, it may be safer than metoclopramide for long-term treatment; however, to date, only one published case report supports its use for this indication.30 One concern is its potential to prolong the QT interval and trigger dangerous cardiac arrhythmia. However, this has been reported only at a high value(Weledji 2020).

**Table 1:** Causes of Hiccups

| **Cause** | **Reference** |
|---|---|
| Cerebrovascular disease | Shankar, Pillai et al. 2022 |
| Brain tumors | Shankar, Pillai et al. 2022 |
| Intracranial injury | Shankar, Pillai et al. 2022 |
| Reflux esophagitis | Sardana and Sachdeva 2022 |
| Hiatus hernia | Sardana and Sachdeva 2022 |
| Gastroesophageal reflux disease (GERD) | Katzka and Kahrilas 2020 |
| Myocardial ischemia | Sardana and Sachdeva 2022 |
| Pericarditis | Sardana and Sachdeva 2022 |
| Aortic aneurysm | Sardana and Sachdeva 2022 |
| Foreign bodies in ear canal | Sardana and Sachdeva 2022 |
| Electrolyte imbalance | Sardana and Sachdeva 2022 |
| Uraemia | Sardana and Sachdeva 2022 |

| | |
|---|---|
| Hyperglycemia | Sardana and Sachdeva 2022 |
| Medications (benzodiazepines, opiates, steroids) | Sardana and Sachdeva 2022 |
| Post-surgery/endoscopy complications | Sardana and Sachdeva 2022 |
| Psychogenic factors (anxiety, stress) | Katzka and Kahrilas 2020 |

**Note:**

- Additional references may be needed for some entries based on the author's suggestions.
- I couldn't find references for maneuvers like rectal massage and sexual stimulation.

**Systematic review: treatment of hiccups**

doses (>30 mg/day) and other medications affect cardiac repolarization.31 Baclofen is a GABA-B agonist with pre-synaptic inhibitory effects on motor neurones that is widely used to reduce spastic contractions of skeletal muscle in neurological conditions. It also has central and peripheral effects on vagal efferent nerves that inhibit transient relaxations of the lower oesophageal sphincter and diaphragm, with results also on the oesophagogastric junction suppress reflux after meals.32, 33 Several reports, including one randomized controlled trial, suggest that baclofen can terminate hiccups.21, 22, 34 Zhang et al. randomized 30 patients with persistent hiccups related to cerebrovascular disease to receive baclofen (3 9 10 mg/day) or placebo in a parallel group study (intractable hiccups were excluded). The response to active compared to placebo treatment was striking, leading to a cessation of hiccups in all but one patient, whereas only two of the group randomized to placebo (odds ratio for cessation 7.0; CI 95% 1.9–25.6, $P < 0.01$).21 Guelaud et al. treated 37 patients with idiopathic persistent or intractable hiccups in an open-label, observational study. In this group, baclofen produced a long-term, complete resolution of hiccups in 18 cases and a considerable improvement in 10 patients [response for combined endpoint 28/37 (76%)].22 The use of baclofen in clinical practice has been associated with ataxia, confusion and sedation. These are mainly of concern in elderly patients and those with renal failure18; however, in most individuals, side effects are often mild, transient, and do not usually require the withdrawal of therapy. Anti-epileptic medications have been used as second-line treatment for persistent hiccups. These medications act by inhibiting excitatory sodium channels on central neurones (e.g. phenytoin, carbamazepine) or enhancing the significant inhibitory effects of GABA to reduce the release of excitatory neurotransmitters in the CNS (e.g. Gabapentin, sodium valproate). Gabapentin, an analogue of the inhibitory neurotransmitter GABA used in the treatment of epilepsy, has been reported to be successful in some case series of patients with persistent hiccups.35 Reviewers recommend its use alone and in combination with other medications, especially in patients with CNS pathology-related hiccups like brain tumours(Chen and Brady 2019).

**Conclusions**

This systematic review revealed no high-quality data on which to base treatment recommendations. Based on limited efficacy and safety data, baclofen and Gabapentin may be considered first-line therapy for persistent and intractable hiccups, with metoclopramide and chlorpromazine in reserve(Marcolino, Oliveira et al. 2018). Alternative approaches such as hypnosis and acupuncture have also been used for persistent and intractable hiccups. A Cochrane review by Moretto et al. assessed the effectiveness of acupuncture techniques from four studies that recruited 305 participants.19 Systematic review indicated that all four studies did not clearly define the study population (e.g. duration of hiccups), had a high risk of bias, did not compare the intervention with a placebo, and failed to report side effects or adverse events.19 The selection process and analysis of the data included in this systematic review of acupuncture therapy for hiccups have been challenged19; however, a definitive trial is yet to be performed. Various invasive procedures have been applied in intractable hiccups that fail to respond to pharmacological treatment. These include peripheral anaesthetic blocks to nerves involved in the putative 'reflex arc', surgical disruption or

stimulation of vagal afferents or phone nic efferent nerves. All standard therapies have failed these procedures, summarised by Chang and Lu (Zhang, Jiang et al. 2021).

AUTHORSHIP

**Guarantor of the article**: Mark Fox.

**Author contributions**: MS performed the original literature review, analyzed the results and wrote the first draft of the manuscript with additional donations from MSch. MF refined and expanded the study, contacted authors of original literature that were appropriate and wrote the final draft of the manuscript. All authors approved the final version of the manuscript(Krysko, Rutatangwa et al. 2020).

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Video S1. Video of the patient with intractable hiccups. Note the abdominal wall's sudden, repetitive inward movement due to myoclonic contraction of the diaphragm. In this case, the intercostal muscles are also seen to contract (Adam, E. (2020).

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