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Systemic review: the pathogenesis and pharmacological treatment of hiccups

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SUMMARY

Background
Hiccups are familiar to everyone, but remain poorly understood. Acute hiccups can often be terminated by physical manoeuvres. In contrast, persistent and intractable hiccups that continue for days or months are rare, but can be distressing and difficult to treat.

Aim
To review the management of hiccups, including a systematic review of reported efficacy and safety of pharmacological treatments.

Methods
Available articles were identified using three electronic databases in addition to hand searching of published articles. Inclusion criteria were any reports of pharmaceutical therapy of 'hiccup(s)', 'hiccough(s)' or 'singultus' in English or German.

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, systematic review revealed no adequately powered, well-designed trials of treatment. The use of baclofen and metoclopramide are supported by small randomised, placebo-controlled trials. Observational data suggest that gabapentin and chlorpromazine are also effective. Baclofen and gabapentin are less likely than standard neuroleptic agents to cause side effects during long-term therapy.

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 as first line therapy for persistent and intractable hiccups, with metoclopramide and chlorpromazine in reserve.

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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 intake of air that is, within a few milliseconds, interrupted by closure of the glottis. It is this that results in the characteristic sound, the 'hic' in hiccups, 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 suggest that it may have a role in training inspiratory muscles in readiness for respiration after delivery.[1, 2]

Epidemiology

The classification of hiccups is based on their duration.[3] An acute attack lasts less than 48 h. 'Persistent hiccups' last more than 2 days. 'Intractable hiccups' are present if the attack lasts more than 1 month. The Guinness Book of Records documents the longest period of continuous hiccupping at 69 years and 9 months. This attack was apparently cured, at last, 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 has 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% of patients with reflux symptoms complain of recurrent hiccups compared to approximately 3% of controls.[5, 6] Overall, the prevalence in 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 condition is difficult to control this impacts on patient's quality of life and mood by interfering with eating, social interaction and sleep.

Pathophysiology

Hiccups are spontaneous, myoclonic[a] contractions of the diaphragm and, in many cases, the intercostal musculature. As first proposed by Bailey in 1943, it 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 und gamma-amino-butyric-acid (GABA-ergic) neurotransmitters can modulate this central mechanism. The efferent response of the reflex is carried by the phrenic nerve 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 an important protective reflex because, without it, in patients with a tracheotomy hiccups lead to significant hyperventilation.[9]

Causes of hiccups

Any process that affects the afferent, central or efferent components of the proposed reflex arc can trigger hiccups. The most common cause is distension of the stomach by a large meal or carbonated drinks. The reflex can be triggered also 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 of these 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; however, it is

[a]Myoclonic contractions are automatic contractions of a muscle or group of muscles leading to organised movement of a limb or, as in the case of hiccups, other body parts. This is distinct from fasciculations that are disorganised contractions of muscle fibres that do not produce movement.

very rare for hiccups to be the single, presenting symptom of serious neurological disease.[2] Peripheral causes are dominated by gastrointestinal diseases. Reflux oesophagitis and the presence of a large hiatus hernia are often cited as causes of persistent hiccups[10]; however, reflux can be the effect as well as the 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 oesophago-gastric junction, all of which favour gastro-oesophageal reflux (GERD; Figure 2). Cardio-vascular disease 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 recognised side effect of medications such as benzodiazepines, opiates and steroids. The problem can appear after surgery or endoscopy due to the use of sedation, oro-pharyngeal intubation or distention 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.

Investigation

Searching for the cause of hiccups can be a challenge 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 visualised, then an oesophageal manometry and a 24-h pH-impedance reflux study should be considered as GERD may be the most common trigger of hiccups.[10] If neurological symptoms or signs are identified, then Magnetic Resonance Imaging of the head and neck is the most sensitive method to identify CNS pathology including brainstem and cranial nerves.

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 the treatment of 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 effective in the majority of cases. Notwithstanding the above, recent years have seen new trials and case series enter the literature. Regulatory bodies have also published new recommendations concerning the use of pharmacological agents for this indication.

AIMS

In the 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.

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 by pharmacological therapy. Initial review revealed only two randomised comparisons of active treatment with placebo or standard care. Thus, the search was expanded to include also outcomes of therapy in case series and other reports of treatment 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 interest to future practice.

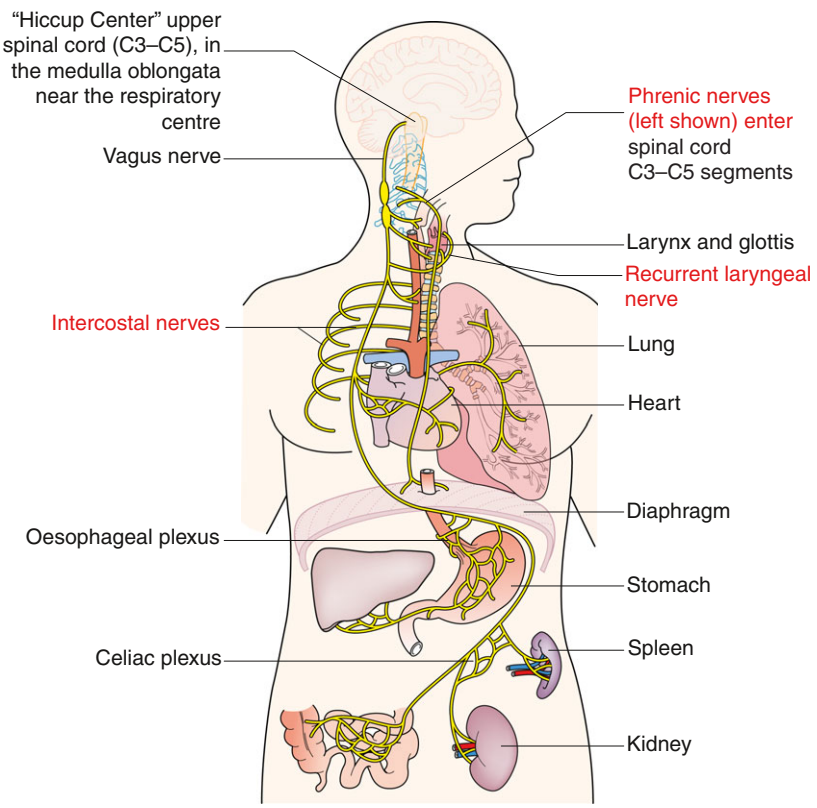

Figure 1 | Anatomy of the hiccups reflux arc (after Bailey 1943). Pathology affecting the brain, diaphragm, thoracic or abdominal viscera can stimulate vagal or phrenic afferents the activate the diffuse 'hiccup center' in the midbrain, brainstem and proximal cervical cord (Table 1). This triggers repetitive 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/or expert opinion in reviews. A comprehensive list of all agents with putative efficacy in hiccups is provided by previous reviewers.[2, 8, 12, 13] Levels of evidence and grades of recommendations are based on those proposed by the Oxford Center for Evidence Based Medicine (cebm.net).

RESULTS

Description of included studies

A total of 341 patients with persistent or intractable hiccups received empirical pharmacological therapy with the results 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 randomised controlled studies have been performed, one for metoclopramide (n = 36) and one for baclofen (n = 30). In addition 13 case series (n = 4–50) were identified. Some were prospective, reporting on the effects of treatment in patients referred for investigation and treatment, others were retrospective case note reviews. The standard of reporting was varied (detailed below). A number of 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 disregarding 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 large clinical case series by Cabane *et al.* into use of proton pump inhibitors (PPI) in patients with hiccups related to GERD.[10] 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 effects of PPI in the empirical management of hiccups; however, this study was included because baclofen or

Table 1 | Frequent causes of persistent and intractable hiccups

Central nervous system			
Vascular	**Infectious**	**Structural**	**Other**
Ischaemic/haemorrhagic cerebrovascular insult	Meningitis	Brain injury	Neuromyelitis optica
	Encephalitis	Intracranial tumour	Parkinson's Syndrome
			Epilepsy, Multiple Sclerosis

Peripheral nervous system (phrenic, vagal and sympathetic nerves)		
Gastrointestinal	**Thoracic**	**Ear, nose and throat**
Gastro-oesophageal reflux disease	Cardiovascular	Herpes zoster
Hiatus hernia	Myocardial ischaemia	Rhinitis
Oesophagus cancer	Pericarditis	Otitis
Stomach distension	Thoracic aneurysm	Pharyngitis
Peptic ulceration	Pulmonary	Foreign body in nose or ear
Pancreatitis	Bronchitis	
Abdominal abscess	Pneumonia	
Abdominal tumours	Asthma	
Bowel obstruction	Bronchial carcinoma	
	Tuberculosis	

Other causes			
Toxic metabolic	**Pharmacologic**	**Surgical**	**Psychosomatic**
Hyponatremia	Steroids	Pharyngeal intubation	Anxiety
Hypokalemia	Dopamine agonists	Anaesthetic agents	Excitement
Hypocalcemia	Chemotherapy (platinum based agents)	Thoracic and upper abdominal surgical	Stress
Hypocapnia	Benzodiazepines	Endoscopy	Fear
Renal impairment	Opioids	Placement of central venous catheter	
Diabetes mellitus	Barbiturate		
Alcohol	Antibiotics (e.g. macrolides)		

gabapentin was administered as part of a combination treatment. Additionally, several patients had received PPI before referral without benefit.[16, 17]

Patient characteristics

Persistent and intractable hiccups were defined by Kolodzik *et al.* in 1991.[3] In earlier case series and in 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 not possible to verify that all patients included in all studies had more than 48 h continuous hiccups prior to treatment. Note that we included studies that recruited patients that did not have hiccups all the time, but 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 gastroenterologists reported treatment of hiccups related to gastrointestinal disorders. Neurologists reported 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 efficacy of second-line medications (e.g. anticonvulsants) limited recruitment to individuals that had not responded to other medications 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 renally excreted drug are increased in this group.[18] In others papers patients with severe co-morbidity and/or psychiatric disorders were excluded due to concerns about drug interactions or exacerbation of neurological symptoms.

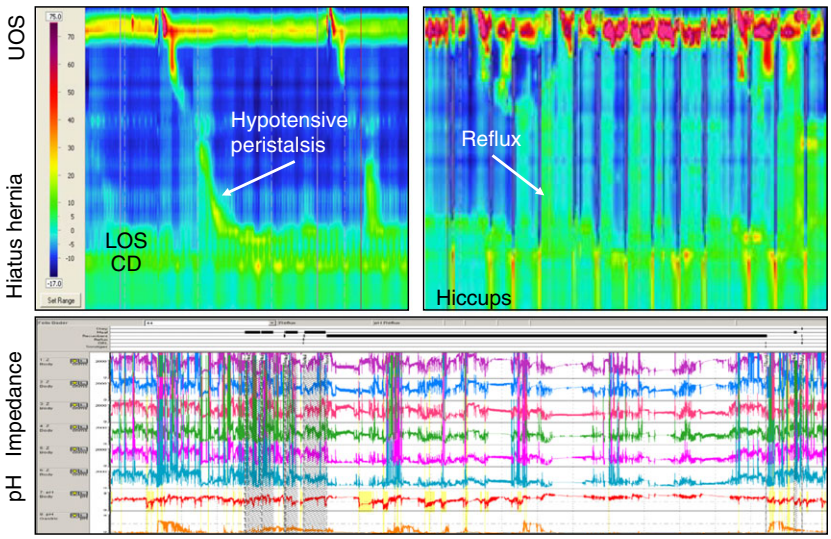

Figure 2 | Oesophageal function before and during an acute attack of hiccups in a patient with hiatus hernia and gastro-oesophageal reflux disease. High resolution manometry demonstrates characteristic short contractions of the crural diaphragm during hiccups. Note suppression of peristalsis and lower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

Table 2 | Physical therapy of hiccups

Nasopharyngeal stimulation	Vagal stimulation	Respiratory manoeuvres
Intra-nasal application of vinegar	Cold compress to face	Breath hold (inspiration, expiration)
Inhalation of 'smelling salts' or similar stimulant/irritant (e.g. ammonia, ether)	Carotid massage	Re-breathing (hypercapnea)
Oro-pharyngeal stimulation (e.g. ice water)	Induced fright	Valsalva manoeuvres
	Induced vomiting	CPAP-respiration

These manoeuvres are, in general, effective only to foreshorten an attack of acute hiccups and not in the treatment of persistent or intractable hiccups. None have been subjected to clinical trials (level of evidence IV, grade of recommendation C).

Therapeutic intervention

Several pharmacological agents are reported to have efficacy for 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 certain that this represents a positive write up and/or publication bias (not formally tested).

Two large case series from the 1950s document the efficacy of intravenous chlorpromazine for 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 route of delivery 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.

The use of metoclopramide and baclofen are each supported by a randomised, placebo-controlled parallel group trial and at least one larger case series. Observational data from case series suggest that gabapentin is also effective. Similar to the patient characteristics, the

Table 3 | Systematic review: pharmacological treatment of persistent and intractable hiccups

Author (year) Study type	Participants	Medication (dose × frequency)	Endpoints	Success (%)	Adverse events	Notes
Wang[20] Multicenter, double-blind, randomised, controlled parallel group trial	Hiccups secondary to cancer, cerebrovascular disease (n = 36)	Metoclopramide (M) 3 × 10 mg/day or Placebo (P), Duration 15 days	Primary – Overall efficacy *Secondary* Cessation Improvement (reduction in frequency and severity)	Overall efficacy M: 11/17 (65) P: 4/17 (24). RR 2.8 95% CI: 1.1 . . . 6.9, P = 0.03 Cessation M: 2/17 (12) P: 0/17 (0) Improvement M: 9/17 (53) P: 4/17 (24)	Fatigue (47%), Mood disturbance (35%), Dizziness (29%), Constipation (18%)	Pilot study relatively small sample Primary endpoint includes subjective assessment Few participants achieve cessation
Madanagopolan[39] Case series	Idiopathic and secondary hiccups (n = 14)	Metoclopramide 10 mg oral or 5–10 mg intramuscularly or intravenously every 8 h	Improvement	14/14	None	Short report only Subjective end point (not fully defined)
Zhang[21] Double-blind randomised, controlled, parallel group study	Secondary to cerebrovascular disease with persistent hiccups (n = 30)	*Baclofen (B)* 3 × 10 mg/day, or Placebo (P) 3× day for 5 days	Cessation	Cessation B: 14/15 (93) P: 2/15 (13) RR 7.00; 95% CI: 1.9–25.6, P < 0.01	Transient Drowsiness (1), Dizziness (1)	Pilot study relatively small sample Restricted to stroke patients Intractable hiccups excluded
Mirijello (2013) Case series	Idiopathic and secondary hiccups (n = 7)	*Baclofen (B)* 10 mg/single administration	Cessation	7/7 (100)	None reported	Not clear if all had persistent or intractable hiccups
Ramirez[34] Double-blind randomised, controlled, crossover study	Idiopathic hiccups resistant to other drugs. Exclusions: organic GI disease, depression, renal insufficiency (n = 4)	*Baclofen* 3 × 5 mg/day for 3 days, then 3 × 10 mg/day for 3 days, tapering to zero for 4 days or Placebo	Improvement (subjective severity and hiccup-free periods)	4/4 (100), P = 0.03	None	Short report only Small sample size Subjective end point. Cessation not achieved
Gueland[22] Case series	Idiopathic (n = 17) or secondary to gastro-oesophageal disease (n = 20)	*Baclofen* 15–75 mg/day (commence 15 mg/day in divided doses, increasing by 15 mg/day until max. 75 mg/day)	Complete resolution (CR) Partial resolution (PR; change from continuous to intermittent hiccup, 50% decrease in frequency and/or intensity Treatment failure (TF)	CR 18/34 (53) PR 10/34 (29) TF 6/34 (18)	Only observed at doses >45 mg/day: Nausea, Somnolence	Doses ranging 15–75 mg/day Subjective end points

Table 3 | (Continued)

Author (year) Study type	Participants	Medication (dose × frequency)	Endpoints	Success (%)	Adverse events	Notes
Petroianu[16, 17] Case series	Idiopathic (n = 29)	Step 1. *Baclofen* 45 mg/day and *Cisapride* 30 mg/day and *Omeprazole* 20 mg/day *Only if step 1 failed* Step 2. *Gabapentin* 1200 mg/day and *Cisapride* 30 mg/day and *Omeprazole* 20 mg/day	Complete resolution (CR); Partial resolution (PR; decrease in frequency/intensity)	Step 1. B/C/O: CR 11/29 (38) PR 7/29 (24) Step 2. G/C/O: CR 1/10 (10) PR 2/10 (20)	Not reported	Step 2 applied only if Step 1 not successful In part, subjective end point
Porzio[7] Case series	Secondary to cancer (n = 43)	Gabapentin 900–1200 mg/day	Complete resolution (CR) Partial resolution (PR) Treatment failure (TF)	CR 35/41 (85) PR 6/41 (15) TF: 2/41 (18)	Transient sleepiness (2/41)	
Moretti *et al.*[40] Case series	Secondary to cerebrovascular disease (n = 8)	*Gabapentin* 1200 mg/day for 3 days, then 400 mg/day for 3 days	Improvement	8/8 (100)	Not reported	Subjective end point (not fully defined) Described in authors review
Thompson[35] Case series	Idiopathic and secondary causes (n = 17)	*Gabapentin* 200–1200 mg/day, duration 1 day – continuous use	Cessation	17/17 (100)	Not reported	9/17 cases often combined with other medication
Friedgood[15] Case series	Idiopathic (n = 3) Secondary to surgery/anaesthetics (n = 27), medical condition (n = 20) Patients not responsive to other treatment (n = 50)	Chlorpromazine 25–50 mg intravenous, repeated in 2–4 h	Cessation	41/50 (82)	Hypotension, sedation, skin rash, central nervous depression	Short Report only Not clear if all had persistent or intractable hiccups
Davignon[14] Case series	Heterogeneous (n = 50)	Chlorpromazine 25–50 mg intravenously	Cessation	40/50 (80)	Postural hypotension, sedation	Short report only
Jacobson[41] Case series	Associated with different organic problems (n = 5)	Valproic acid started with 15 mg/kg/day, increased by 250 mg every 2 weeks until success or adverse events	Cessation Improvement (not fully defined)	4/5 (80)	GI bleeding (n = 1)	Short report only Possibility of valproate-induced hepatotoxicity

Table 3 | (Continued)

Author (year) Study type	Participants	Medication (dose × frequency)	Endpoints	Success (%)	Adverse events	Notes
McFarling[42] Case series	Multiple sclerosis (n = 4)	Carbamazepine 4 × 200 mg/day	Cessation	1/4 (25)	Not reported	Letter only
Lipps[43] Case series	Idiopathic (n = 2), associated with surgery (n = 1), medical disease (n = 4)	Nifedipine 20–60 mg/day	Complete resolution (CR) Partial resolution (PR) Treatment failure (TF)	CR: 4/7 (57) PR: 1/7 (14) TF: 2/7 (29)	Bloating, dizziness, mild hypotension (n = 2)	Abstract only High recurrence rate after stop nifedipine Frequent adverse events

choice of medications was clearly related to the speciality of the authors. General physicians and gastroenterologists 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, for example, gabapentin is effective for hiccups related to CNS disease is relatively strong, whereas for hiccups related to gastrointestinal pathology it is limited.

Several studies have documented the effect of acupuncture therapy in patients with hiccups and were summarised by a Cochrane review.[19] Other nonpharmacological therapies that have been subjected to formal assessment include positive pressure ventilation, hypnosis and surgical procedures to disrupt or stimulate nerves involved in the 'reflex arc' (see recent review[2]). All these nonpharmacological approaches may be effective but none are supported by high quality data.

Choice of outcome measures

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

Reporting of side effects

Sedation and other neurological side effects (e.g. fatigue, sedation, dizziness) were not reported by all studies; however, it is clear that these can be associated with all medications with efficacy in hiccups. When reported, the frequency of side effects was up to 50% for neuroleptic medications and this appeared to be more frequent for chlorpromazine[15] and metoclopramide[20] than for baclofen at standard doses[21, 22] or gabapentin.[7] Very little data was available for other medications.

Limitations of the data

There are important limitations to the evidence base supporting the use of 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 of persistent hiccups should be directed at the underlying cause of the condition. This could be as simple as treatment of reflux disease with proton pump inhibitors, or as complex as major 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 treatments have been described for the treatment of hiccups. However, our literature search revealed only two randomised 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. Physiological studies

Table 4 | 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 italic script are noted as alternatives to more established medications

Pharmacological therapy	Level of evidence	Concerns
Recommended (typical dose/day)		Common or important side effects and safety concerns
Baclofen (3 × 5–20 mg/day)	2b	Sedation, renal impairment (in elderly patients with pre-existing disease)
Gabapentin (3 × 300–600 mg/day)	4	Sedation, visual disturbance, clumsiness/unsteadiness
Pregabalin (2 × 75–150 mg/day)	5	*Sedation (less often than gabapentin), breathing difficulties*
Second line		
Metoclopramide (3 × 10 mg)	2b	Neurological and other side effects* *less often than chlorpromazine*
Domperidone (3 × 10 mg)	5	Neurological side effects* *less often than metoclopramide Hyperprolactinemia, long QT syndrome/cardiac arrhythmia*
Third line		
Chlorpromazine up to 4 × 25–50 mg/day	4	Sedation, postural hypotension (common with iv dosing), neurological and other side effects*
Other choices		
Carbamazepine, 3–4 × 100–300 mg/day	4	Blurred vision, neurological and mood disturbance
Valproate dose titration to 20 mg/kg/day	4	Weight gain, liver failure, neurological and mood disturbance
Phenytoin 3 × 100 mg/day	5	Weight gain, coarse facies, neurological and mood disturbance
Nifedipine 60–180 mg/day	4	Hypotension, headache, peripheral oedema, respiratory effects
Amitriptylline initial 1 × 25–100 mg/night	5	Sedation, dry mouth, constipation, cardiac arrhythmia in overdose *consider if visceral hypersensitivity appears to be causative factor*

Nonpharmacological therapy	Level of evidence	Safety concerns
Hypnosis	5	None
Acupuncture (auricular, classic)	4	Transmission of infection by use of unsterilised needles
Nerve block (C3–C5, phrenic, vagal nerve)	5	Nerve damage, pneumothorax, diaphragmatic paresis
Implantation of vagal nerve stimulator or similar neuromodulation device	5	Risks of surgery, nerve damage, unwanted side effects of vagal stimulation/dysfunction

* Neurological side effects (acute dystonia, akathisia, tardive dyskinesia), impaired glucose tolerance, weight gain, increased mortality due to thrombotic and cardiovascular events.

have demonstrated a mechanism by which these manoeuvres improve hiccups, with the frequency of hiccups decreasing as arterial pCO_2 rises.[9] This experimental evidence, backed up by personal experience of the senior author, suggests that an effective method to interrupt hiccups is to hold ones breath in expiration (diaphragm relaxed, pCO2 high). Other techniques that can lead to 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 help[24, 25]; however, we recommend that this kind of recommendation is reserved for carefully selected patients!

A wide range of pharmacological treatments has been used to terminate persistent and intractable hiccups (Table 3). 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', whereas high doses have a general inhibitory effect and suppress repetitive contractions. In the absence of comparative studies, the choice of medication should take into account any underlying cause, the medical status of the patient and possible side effects. For example, in gastroenterological practice, symptoms of reflux disease are common in patients referred 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 and effective in a large observational study.[10]

In the past, the class of medications most often used to treat hiccups are phenothiazine neuroleptics. 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 by specific effects on particular neurotransmitters. The use of chlorpromazine is supported by two large case series (both $n = 50$) 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. Furthermore, this agent is no longer available in certain countries due to commercial and medical reasons. Similar neuroleptics (e.g. haloperidol, olanzipine) can also be effective at controlling hiccups; however, their use is also limited by side effects such as dizziness, mood disturbance and sedation.[27, 28]

Metoclopramide is a benzamide that shares a similar chemical structure to neuroleptic agents; however, it is less sedative and has important effects on dopamine (D3 antagonist) and serotinergic (5-HT4 agonist) receptors with both central antiemetic and peripheral prokinetic effects. The latter may be useful in hiccups because promoting gastric emptying reduces both gastric distension and GERD. The use of metoclopramide is supported by reviewers, case reports and one recent, randomised controlled trial.[8, 12, 20] Wang and Wang randomised 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 end point 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. Of more concern to patients with intractable hiccups is the risk of long-term dyskinesia when metoclopramide is given as maintenance therapy over a longer period of time.[29] Domperidone is a dopamine antagonist that shares many of the peripheral actions of metoclopramide but does not cross the blood-brain barrier and has very 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 high doses (>30 mg/day) and/or in combination with other medications with effects on cardiac repolarisation.[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 has also central and peripheral effects on vagal efferent nerves that inhibit transient relaxations of the lower oesophageal sphincter and diaphragm with effects also on the oesophago-gastric junction that suppress reflux after meals.[32, 33] Several reports, including one randomised controlled trial, suggest that baclofen can terminate hiccups.[21, 22, 34] Zhang *et al.* randomised 30 patients with persistent hiccups related to cerebrovascular disease to receive baclofen (3×10 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 cessation of hiccups in all but one patient, whereas this happened in only two of the group randomised to placebo (odds ratio for cessation 7.0; CI 95% 1.9–25.6, $P < 0.01$).[21] Guelaud *et al.* treated a series of 37 patients with idiopathic persistent or intractable hiccups in an open label, observational study. In this group, baclofen produced long-term, complete resolution of hiccups in 18 cases and a considerable improvement in further 10 cases [response for combined end point 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 failure[18]; however, in most individuals, side effects are often mild, transient and do not often require withdrawal of therapy.[10, 22]

Anti-epileptic medications have been used as second-line treatment of persistent hiccups. These medications act by inhibiting excitatory sodium channels on central neurones (e.g. phenytoin, carbamazepine) or enhancing the central 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 a number of case series of patients with persistent hiccups.[35] Reviewers recommend its use, alone and in combination with other medications, especially in patients with hiccups related to CNS pathology such as brain tumours.[2] The side effect profile appears to be less problematic that other anti-epileptic agents; however, dizziness and sedation can occur.[35] The efficacy of pregabalin, another GABA-analogue, in the treatment of hiccups has been reported in one case report.[12] This may

be a useful alternative as it has a relatively high bioavailability and is associated with less side effects than Gabapentin in the treatment of chronic pain syndromes.[36]

Other pharmacological treatments include the use of carvedilol, amphetamines and amitriptyline (full list available in other reviews[2, 8, 12, 13]). The mechanism of effect for these agents is speculative and their use is not generally recommended. High-dose benzodiazepines have been used in individual cases for the suppression of treatment-resistant hiccups. Although small doses of benzodiazepines can trigger hiccups,[26] high doses delivered by sub-cutaneous or intravenous infusion can suppress the repetitive, myoclonic contractions of the diaphragm.[37, 38] Occasionally pharmacological 'interruption' of hiccups can provide lasting relief. However, unless the underlying cause is treated, intractable hiccups often return after the benzodiazepine infusion is withdrawn.

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 different 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 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 has been challenged[19]; however, a definitive trial is yet to be performed.

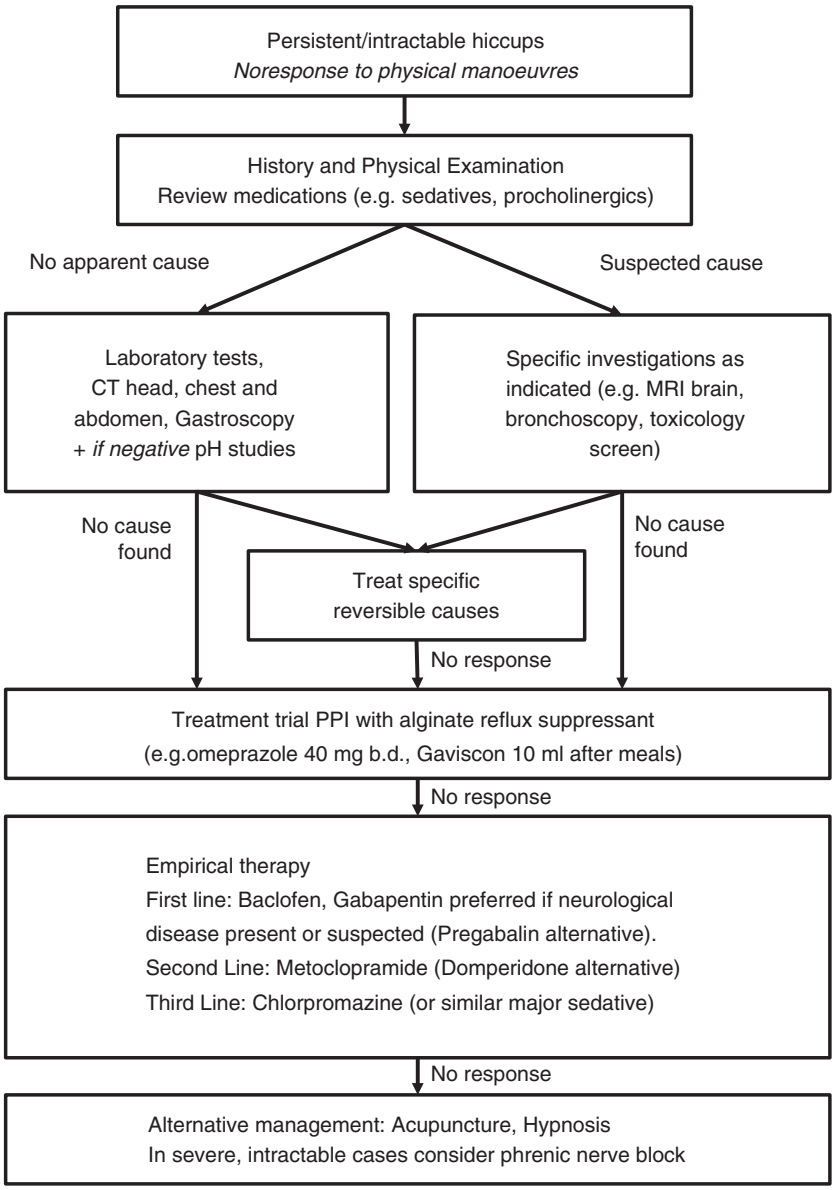

Figure 3 | Treatment algorithm: clinical investigation and management of persistent and intractable hiccups.

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In intractable cases of hiccups that fail to respond to pharmacological therapy a variety of invasive procedures have been applied. These include peripheral anaesthetic blocks to nerves involved in the putative 'reflex arc', surgical disruption or stimulation of vagal afferents or phrenic efferent nerves. These procedures, summarised by Chang and Lu,[2] should be reserved for use in research studies or as 'a final resort' in patients in which hiccups are causing real suffering and in whom all standard therapies have failed.

SUMMARY

Hiccups are familiar to everyone but remain a medical oddity. Acute hiccups that last a few minutes are very common, self-limiting and can often be terminated by simple physical manoeuvres. In contrast, persistent and intractable hiccups that continue for days or months are rare but can be distressing and difficult to treat. If a cause is evident, then this should be treated. If no cause is found, then empirical treatment to suppress GERD provides relief in some individuals. If this fails then pharmacological agents directed at dopaminergic and GABA-ergic receptors may provide benefit. Although this systematic review reveals a lack of adequately powered, well-designed trials, the use of baclofen and metoclopramide for treatment of persistent or intractable hiccups are both supported by small randomised, placebo-controlled trials of treatment. Observational studies indicate that gabapentin and chlorpromazine can also be effective.

Clinical decisions regarding the use of these medications should take into account also recommendations from the FDA and other regulatory bodies that highlight the risk of long-term neurological and other side effects from phenothiazides and related medications. Taking all available evidence into account, we recommend a treatment algorithm (Figure 3) with baclofen as first line therapy for persistent and intractable hiccups. Gabapentin may also be safe and effective in long-term management of this condition, especially for patients with CNS disease. The use of metoclopramide for hiccups is no longer recommended for long-term treatment. Clinical experience also supports the use of chlorpromazine and other neuroleptics for acute, but not long-term management. Looking ahead, large, multi-centre studies will be required to build an adequate evidence base for the treatment of persistent and intractable hiccups. Until then guidelines will continue to be based on somewhat unreliable data and clinical experience.

AUTHORSHIP

Guarantor of the article: Mark Fox.

Author contributions: MS performed the original literature review, analysed the results and wrote the first draft of the manuscript with additional contributions from MSch. MF refined and expanded the review, contacted authors of original literature were appropriate and wrote the final draft of the manuscript. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

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

Video S1. Video of patient with intractable hiccups. Note the sudden, repetitive inward movement of the abdominal wall due to myoclonic contraction of the diaphragm. In this case the intercostal muscles are seen to contract as well.

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