REVIEW ARTICLE

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Approach and Management of Chronic Hiccups – A Common but Difficult Entity

ABSTRACT

Hiccups are quite common and often troublesome for patients and even for physicians as approach and management are not thoroughly clear. This review discusses about hiccups from epidemiology, classification, etiologies, mechanism involved, approach to patient, home remedies to pharmacological drugs to tackle the hiccups. In majority of cases underlying pathology is quite not clear when patient presents with hiccups of more than 48 h duration. It is advisable to start proton pump inhibitors as initial drug of choice as gastroesophageal reflux diseases are found to be most common underlying etiology for hiccups. Treatment should be changed or combination therapy should be initiated if patient is not responding to first line agent after 1–2 weeks. Weightage should be given to associated symptoms with hiccups as they guide to pathology there is a lack of strong evidence based pharmacological and surgical data that suggests an effective step wise solution to this common problem. Large patient-controlled trials are necessary for alternative therapies like acupuncture and hypnosis to place them in proper management plan with enough evidence.

Key words: Hiccups, Gastrointestinal reflux disease, Vagus nerve, Phxnic nerve

INTRODUCTION

Hiccups are contractions of diaphragm resulting in "hic" sound. It is taken from Latin word "*Singult*," which means "catch of breath while sobbing"[1] The longest reported hiccups case from Guinness Book of World Records was for 69 years and 9 months in a farmer from Iowa[2] Hiccups remain a poorly understood phenomenon, despite the years of medical progress. Treatment differs among the treating physicians or gastroenterologists. We review the etiologies, diagnostic modalities, and management of hiccups with the current evidence in literature.

CLASSIFICATION

Acute hiccups are of <48 h duration, *persistent hiccups* last over 48 h–1 month and *intractable* last more than a month.[3] In day-to-day life, acute hiccups do not require any treatment as they don't have any specific reason to start and disappear within a few minutes. Persistent and intractable hiccups are generally associated with a pathological disease process.[4]

EPIDEMIOLOGY

Incidence of Hiccups is 4723 (SD ± 937) hospitalizations per year and an incidence of 632 cases per million hospital discharges[5] Men have higher prevalence (91%) of intractable hiccups than women and are mostly seen with age over 50 years.[4]

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Patients with disorders of the central nervous system (CNS) such as Parkinson's disease (20%), frequently report hiccups than the general population[3,6] Approximately, 8–10% patients had hiccups with underlying gastroesophageal reflux disease (GERD)[3,6] Organic causes should be ruled out before labelling psychogenic.[7] There are no racial, geographic, or socioeconomic variation in hiccups.

PATHOPHYSIOLOGY

Hiccups are controlled by a complex reflex arc consisting of three main components: the afferent limb, processing in the CNS, and the efferent pathway. The afferent limb is made up of the vagal, phrenic, and sympathetic nerves from T6 to T12 that relay somatic and visceral sensory information to the central midbrain.[1,8,9] Brainstem and cervical spine make the main processing component of CNS, which is the second aspect of reflex arc. The third portion, the efferent limb of the reflex arc contains the phrenic nerve (C3-C5) innervating the diaphragm, anterior scalene muscle innervation (C5-C7),

recurrent laryngeal nerve, and accessory nerves leading to the intercostal muscles (T1-T11)[1,3,10,11] [Figure 1]. Hypothalamus, brainstem or cervical spinal cord pathology may induce hiccups by stimulating the hiccups reflex or decreasing the normal inhibition of the neurons involved.[9]

Multiple neurotransmitters are involved including GABA, dopamine, serotonin, glutamate, glycine, histamine, epinephrine, and acetylcholine [Table 1]. Epinephrine, norepinephrine, acetylcholine, and histamine are responsible for peripheral signalling.[6,8,9,12] Table 2 shows nerves involved in hiccups as per the etiologies.

ETIOLOGY OF HICCUPS

Disruption of afferent, central, or efferent components of reflex arc could precipitate hiccups. Hiccup bouts of <48 h duration typically are benign generally. By contrast, hiccups lasting >48 h occur rarely and may be caused by a serious underlying disease.[1,11]

Most etiologies of prolonged hiccups are structural, infectious, or inflammatory disorders that impact either the CNS or the vagus or phrenic nerves or their branches.[11] Potential causes of persistent and intractable hiccups are shown in a Table 3.

The most common cause of hiccup is gastric reflux and distension[7] and about 80% of patients with persistent hiccups seen in evaluation may be attributable to GERD.[3]

Peripheral causes

Any peripheral irritation that affects the reflex arc can potentially cause a hiccup.

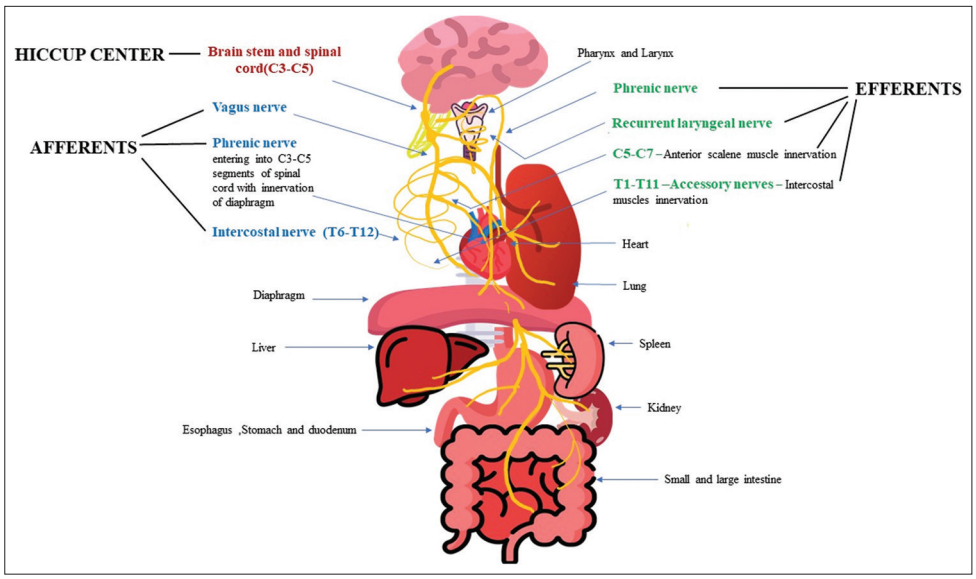


Figure 1: Hiccup Reflex arc showing afferents, hiccup centre and efferents with mechanism of hiccups

Table 1: Neurotransmitters and their significance in hiccups

Neurotransmitter	Drug involved in hiccups	Treatment	Supporting evidence
Dopamine	Aripiprazole (70) Dopamine agonist (71) (Piribedil, pergolide, pramipexole)	Metoclopramide (72) Chlorpromazine (73) Baclofen, clonazepam (73)	Aripiprazole reported to cause hiccups (70) Higher incidence of hiccups in Parkinson's disease patients (74)
Gamma amino butyric acid	Propofol Benzodiazepines (75)	Baclofen, valproic acid (76)	Nucleus raphe GABA-associated inhibition of hiccups in cats (77)
Serotonin	-	Olanzapine (78), Sertraline (79) Risperidone (80)	Involved in vagal afferents and gut enterochromaffin (12)
Histamine	-	Omeprazole (81)	Thought to decrease afferent hiccup reflex stimulation (81)
Epinephrine and Norepinephrine	-	Methylphenidate (82)	Methylphenidate successfully treated intractable hiccup in lung cancer patient (82)
Acetyl choline	-	Metoclopramide (76)	Acetyl choline responsible for oesophageal contraction there by metoclopramide act by reducing oesophageal contractions (76)

Table 2: Nerves involved in hiccups according to etiology

Nerves	Aetiology
Phrenic Nerve	Goitre
	Mediastinal tumour
	Tumour/Cyst in neck
	Diaphragmatic abnormalities
Recurrent laryngeal nerve, Branch of vagus nerve	Pharyngitis
	Tumour in neck
	Laryngitis
Auricular branch of vagus nerve	Foreign body in external auditory canal (Example. Hair)

Gastrointestinal (GI)

In most recent data collected from 14 years of hiccups in USA, common causes of hiccups were following –GERD (GERD – 23.1%), diverticular disease, intestinal obstructions, adhesions, and rectal carcinoma.[5] GERD causing hiccups usually responds to proton pump inhibitors (PPI).[12] Hiatus hernias may precipitates persistent hiccups. Manometry and pH-impedance revealed that hiccups could inhibit normal esophageal motility and reduce lower esophageal sphincter tone.[3]

Overeating, consumption of carbonated beverages, aerophagia (swallowing air while chewing gum or smoking), or gastric insufflation during endoscopy all can cause gastric distention and can lead to hiccups.[13] Diet has an influence on hiccups as hot or cold liquids, alcohol, and spicy foods tend to be more likely to cause hiccups.[1,6,14]

Thoracic and cardiac

Myocardial infarction and pericarditis are most common cardiac causes of hiccups.[15] Enlarged lymph nodes (due to a neoplasm or infection), aortic aneurysm, chest trauma, pneumonia, empyema, bronchitis, pleuritis, and mediastinitis, rarely pulmonary embolism might cause hiccups.

Ear, nose, and throat

Phrenic nerve irritation along its course by goiter, tumor, cyst in the neck, a mediastinal mass, and diaphragm abnormalities can cause hiccups.[1,3,16] Pharyngitis, laryngitis, or by a tumor in the neck may irritate recurrent laryngeal nerve, a branch of the vagus and cause hiccups. Foreign body in the external auditory canal can lead to hiccups in some cases (e.g., a hair) by irritation of the auricular branch of vagus nerve.[1,17]

Surgical

Iatrogenic causes of hiccups include introduction of central venous lines, bronchoscopy, and trans-venous pacing pharyngeal intubation, endoscopy of upper GI tract.[1] Persistent hiccups was reported with suprahepatic inferior vena cava (IVC) stenting for IVC stenosis in case of primary Budd-Chiari syndrome which responded to baclofen.[18]

Post-operative

In the post-operative setting, studies suggest an association with phrenic nerve irritation with hiccups. Causes might be related to general anesthesia, neck extension, and traction of viscera. In a retrospective study of 30 years at a large medical center, among 40 cases of post-operative hiccups, 31 occurred after surgery along the distribution of the phrenic nerve (CNS [seven cases], intrathoracic [one case], and intra-abdominal [23 cases]).[19]

Toxin and metabolites

Multiple metabolic derangements could produce hiccups by hypocapnia, hypocalcaemia, hypokalaemia, hyponatremia, and uraemia. Chronic renal failure or diabetes mellitus could also contribute to the onset of hiccups by producing uraemia and GI dysmotility respectively.[1,11]

Infections

CNS infections such as neurosyphilis, tuberculosis, Herpes Zoster virus, herpes simplex virus, have been reported to cause hiccups in multiple case series.[1,3] In the pandemic of COVID-19, case series and meta-analysis have shown 16 patients with persistent hiccups as a presenting complains of COVID-19 infections and who resolved with conservative management.[20-23]

Drugs

Certain medications could cause hiccups by affecting the CNS or the vagus or phrenic nerves. Dexamethasone is known to cause hiccups with unknown mechanisms. Switching from dexamethasone to methylprednisolone for patients on chemotherapy could relieve the hiccups.[8] Pharmacologic basis showed reduction the threshold of synaptic transmission in the midbrain and allow for easier stimulation of the reflux.[11]

Other medications associated with hiccups are diazepam, midazolam, barbiturates, tramadol, certain anti-cancer drugs (e.g., levofolinate, fluorouracil, oxaliplatin, carboplatin, and irinotecan) and alpha methyldopa.[24,25] A rare case has been reported for protracted Hiccups following Aripiprazole which responded with Gabapentin.[26]

Psychosomatic

Psychogenic causes of hiccups are diagnosis of exclusion. Persistence hiccups during sleep are usually found with organic cause and is a key factor to differentiate between psychogenic and organic causes of hiccups.[27] Psychogenic factors associated with hiccups include anxiety, stress, excitement, and malingering, anorexia nervosa, schizophrenia and conversion disorder.

Central causes

Any disruption of the hiccups reflex arc by lesions in the brain can cause symptom. Cerebral vascular accidents and other vascular defects such as aneurysms have been shown to be

Table 3: Etiology of hiccups

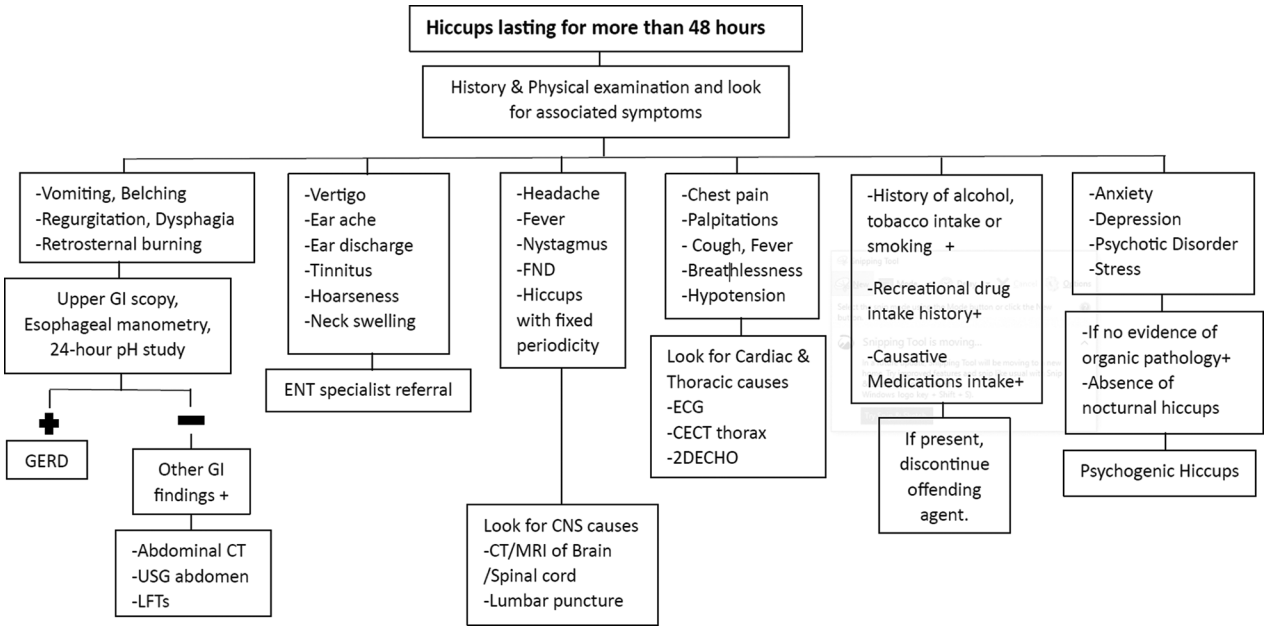
Central causes			
Vascular	Infectious	Structural	Others
Ischaemic/haemorrhagic stroke Arterio-venous malformation Temporal arteritis	Meningitis Encephalitis Brain abscess	Brain injury Intracranial tumour Hydrocephalus syringomyelia	Neuromyelitis Optica Parkinson's Syndrome Epilepsy Multiple Sclerosis
Peripheral causes			
Gastrointestinal	Thoracic	Cardiac	Ear, nose and throat
Hiatus hernia Oesophagus cancer Stomach distension Peptic ulceration Pancreatitis Abdominal tumours Abdominal abscess Gallbladder disease Inflammatory bowel disease Hepatitis Aerophagia Bowel obstruction Erosive and eosinophilic esophagitis	Thoracic aneurysm Pleuritis Bronchitis Pneumonia Bronchial carcinoma Tuberculosis Mediastinal lymphadenopathy Mediastinitis Pulmonary embolism	Myocardial ischaemia Pericarditis	Rhinitis Otitis Pharyngitis goitre Foreign body in nose or ear Neck cyst or tumour
Psychosomatic			
Anxiety Schizophrenia Anorexia nervosa	Excitement Stress Fear	Conversion disorder	Malingering
Surgical			
Pharyngeal intubation	Anesthetic agents	Thoracic and upper GI surgery Endoscopy	Placement of central venous catheter
Toxic metabolites			
Hyponatremia Hypokalemia Hypocalcemia Hypocapnia	Diabetes mellitus	Uremia	Alcohol
Postoperative			
General anesthesia	Neck extension (peripheral nerve root stretching)	Intubation (Stimulation of glottis)	Traction on viscera
Drugs			
Steroids Antibiotics	Steroids Antibiotics	Benzodiazepines Benzodiazepines Opioids	Chemotherapy (platinum-based agents)
Infectious			
Subphrenic abscess	Malaria, Tuberculosis	Herpes zoster	Covid 19

correlated with hiccups, and they respond to treatment of CNS lesions.[1]

Other CNS lesions like Arnold-Chiari malformations with cervicothoracic syringomyelia and brain stem tumours, including astrocytoma and cavernomas, neuromyelitis Optica have been described in hiccups, thus implicating the medulla as a central neurogenic mediator of hiccups. Some reports mention antiphospholipid syndrome with infarction of the medulla has been described.[28,29]

DIAGNOSIS

Any episode of hiccups of ≥48 h should be evaluated. With the initial assessment, the patient should be advised to initiate physical maneuvers for symptomatic relief as they may be helpful and are unlikely to cause harm. Here, we have proposed an algorithm for the evaluation of hiccups lasting longer than 48 h [Algorithm 1]. Underlying etiology should be suspected depending on presenting complaints and investigations should



Algorithm 1: Approach to hiccups. GERD: Gastroesophageal reflux disease, GI: Gastrointestinal, CT: Computerised tomography, USG: Ultrasound abdomen, LFT: Liver function tests, ENT: Ear, nose, throat, FND: Focal neurological deficits, ECG: Electrocardiogram, MRI: Magnetic resonance imaging, 2D ECHO: 2-dimensional echocardiography

be guided according to that. A detailed drug history for the potentially causative medication is necessary and should be discontinued to look for improvement.

A history and physical exam may reveal underlying pathology and further investigations should be carried out depending on that. For example, brain imaging for associated neurologic signs and symptoms, chest computed tomography (CT) and X-ray for pulmonary disease, upper GI endoscopy, Oesophageal manometry, and pH impedance if GI pathology is suspected. Alcohol, recreational drug use, and tobacco use have all been linked to chronic hiccups[6] Nocturnal hiccups are usually suggestive of organic pathology, and Hiccups with a fixed periodicity may be suggestive of an intracranial lesion.[19]

When hiccups are not associated with any other complaints, a stepwise approach is best. Obtaining basic blood work (Complete blood counts, metabolic profile, liver function tests), chest X-ray, and electrocardiogram should be included as a part of initial testing. Upper GI endoscopy is a logical next step given that the prevalence of hiccups is related to GERD and associated with GI pathology. CT imaging (chest, neck, ear, nose, and throat) and magnetic resonance imaging (brain) are warranted if all other diagnostic modalities have failed to identify a cause [Algorithm 1]. Most importantly an individualized approach with each patient is required.

For patients with advanced malignancy who develop persistent hiccups, workup is unlikely to alter management, and the cause is often multifactorial. The focus should be on relieving symptoms with medication, rather than on extensive evaluation for other etiologies. Physical maneuvers may be tried.[25]

TREATMENT

Hiccup bouts of <48 h

Typically, not caused by evident pathology and thus do not require evaluation for an etiology.

Prolonged hiccups of >48 h

Usually requires treatment and it should be directed at underlying pathology, though patients should be started on empirical treatment during the evaluation of etiology.

Non-pharmacologic

They range from lifestyle modification and physical maneuvers to invasive procedures. Physical maneuvers can be attempted prior to any pharmacologic treatment as they don't do any harm. More advanced and invasive therapies (nerve blocks/stimulation, acupuncture) should only be considered after failure of pharmacologic management and on a case-by-case basis.

Home remedies

Although not supported by evidence but can be helpful and successful in the termination of hiccups. Stressors that may cause hiccups include eating too much or too quickly, carbonated drinks, spicy foods, being stressed or emotionally excited, drinking alcohol, and being exposed to quick changes in temperature. By avoiding carbonated beverages, and alcohol, avoiding extremes in food temperature, advising to eat slowly, placing a drop of vinegar beneath the tongue,

gargling with water, or sniffing smelling salts, hiccups can be stopped on a homely basis. It is hypothesized that they work by vagal stimulation. These remedies should only be tried in hiccups of <48-h duration.[1,6]

Physical maneuvers

They are simple and generally safe to perform. They are designed to interrupt normal respiratory function to produce hypercapnia, stimulate/irritate the nasopharynx or uvula, increase vagal stimulation, or relieve irritation of the diaphragm.[5] Reports of success are mostly seen in episodes of transient hiccups and efficacy for their use in chronic hiccups is lacking[1] Various physical maneuvers and their potential mechanism to interrupt hiccups have been described in Table 4.[30-32] Recently, the University of Texas Health Science Center in San Antonio has designed and patented an affordable and accessible device that mimics Valsalva called forced inspiratory suction and swallow tool and that was effective in 92% cases.[33]

Acupuncture

By regulating effect on thoracic viscera and GI motility, though local changes to blood flow and modulation of neurotransmitters/inflammation acupuncture are proposed to work in hiccups.[34] A systematic review showed effect of acupuncture in relieving cancer-related hiccups.[35] However, Yue *et al*. reviewed acupuncture use in stroke patients and concluded that because of a limited number of studies and overall poor methodology, no recommendations can be made[36] Despite this, several systematic reviews have failed to show acupuncture as an effective treatment because conclusions cannot be drawn based on the quality of available studies.

Hypnosis

It is safe and can be considered if other modalities of treatment have failed. Two things are necessary before prescribing hypnosis treatments: (1) To exclude any organic etiology and, whenever possible, correct it and (2) to make sure that hypnosis is performed efficiently, including basic knowledge in psychodynamics. In few case reports, persistent hiccups of psychogenic and post operative were terminated by multiple sessions of hypnosis respectively.[37]

Nerve stimulation

Reflex arc intervention can be tried after traditional maneuvers and pharmacologic therapies fail. Surgical placement of a vagus nerve stimulator has been reported as a cure for hiccups in few case reports on stroke patients.[31] Positive effects of might be limited to hiccups of central etiology.

Most of available literature on phrenic nerve blockade for the treatment of hiccups are based on small studies or case reports. In a large series, continuous epidural nerve block at the C3-C5 level in 28 patients achieved a 60% cure with one block and 100% response in hiccups with up to three blocks without any significant adverse events.

Pharmacologic

Pharmacotherapy is indicated in hiccups lasting more than 48 h, unless an etiology that can be quickly corrected is discovered during evaluation (e.g., a foreign body in the external auditory canal). Most of drugs cause modulation in dopaminergic or GABAergic pathways. There is lack of randomized trials to definitively guide the choice among these treatments. Most of the approach is based on observational studies, case reports, and small series that do not directly

Table 4: Physical manoeuvres in hiccups

Method	Potential mechanism
Breath holding for 5–10 s (or as tolerated)	Interruption of respiratory function
While sitting, pulling the knees to chest (or leaning forward to compress the chest), holding for 30–60 s if possible	Interruption of respiratory function
Valsalva maneuver, holding for 5–10 s	Raise in arterial Pco2
Swallowing a teaspoon of dry, granulated sugar	Stimulation of vagus nerve
Uninterrupted drinking	Stimulation of vagus nerve
Tapping over fifth cervical vertebrae	Phrenic nerve disruption
Forceful traction (i.e. pulling) on the tongue	Stimulation of vagus nerve
Biting a lemon	Stimulation of vagus nerve
Carotid massage	Stimulation of vagus nerve
Drinking water through a forced inspiratory suction and swallow device (Rigid tube with a valve that required significant suction effort)	Stimulation of phrenic followed by vagus nerve
Pressing gently but firmly on the eyeballs	Vagal interruption
Inhalation of "smelling salts" or similar stimulant/irritant (e.g. ammonia, ether)	Nasopharyngeal stimulation

compare treatment options.[38] Doses, mechanism of action and side effects of drugs used in treatment of hiccups have been enumerated in Table 5.

An empirical PPI therapy for 3–4 weeks even in the absence of classic reflux symptoms should be considered as first line therapy.

In a prospective cohort study of 37 patients with hiccups for at least seven days; baclofen given as initial treatment produced long-term complete resolution in 55% of cases.[39]

Gabapentin has been used for patients experiencing hiccups while recovering from stroke or in palliative care, and it may be used as a first-line agent for patients with intractable hiccups. It may be used in combination with a PPI, baclofen, or metoclopramide in case of refractory hiccups.[6,11] Pregabalin at a dose of 150 mg orally once daily reduced the frequency and intensity of intractable hiccups, and completely resolved them when the dose was increased to 375 mg daily shown in few case report.[40]

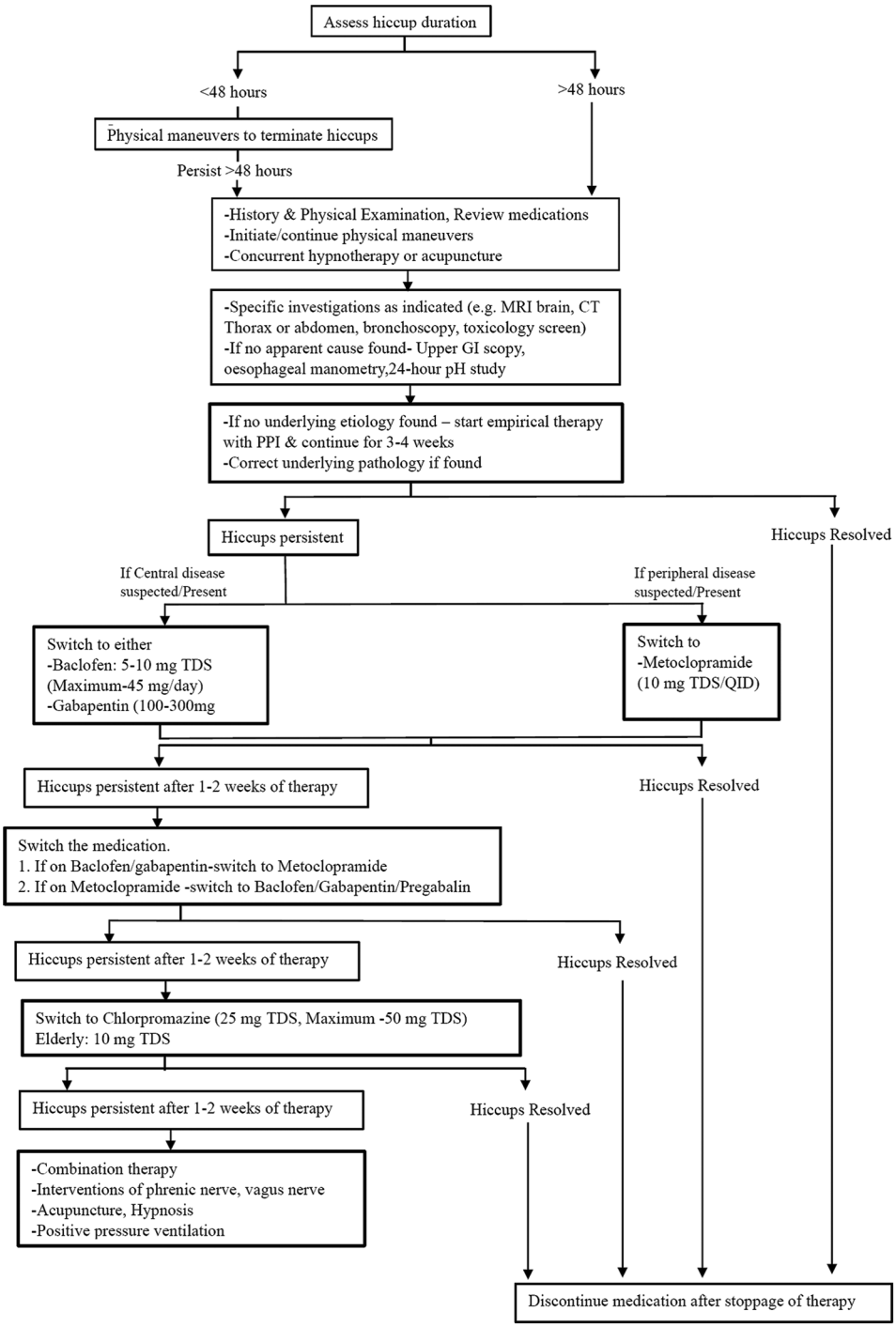
Metoclopramide is usually considered as second line therapy but can be tried as first line in hiccups of peripheral origin.[38] In a randomized controlled trial of 36 patients, metoclopramide was effective in eliminating or improving hiccups compared with placebo (RR 2.75; 95% CI 1.09–6.94).[41,42]

Chlorpromazine is the only drug approved by the US food and drug administration for intractable hiccups, but it is no longer the clear first choice for hiccup treatment. Its use is restricted due to increased mortality in older adult patients who have dementia-related psychosis and long-term use is associated with the risk of tardive dyskinesia. If patient

Table 5: Pharmacotherapy in hiccups

Drug	Dose	Mechanism of action	Importance	Adverse effects
Empirical				
PPI	Standard dosing	Inhibit gastric acid secretion and acidic reflux	Empirical trial if work up is negative/pending -Titrate to bid dosing before considering failure	Generally safe, diarrhoea, osteoporosis on chronic intake
First line				
Baclofen	5–20 mg/day	Inhibition of hiccup reflex arc, GABA-B receptor agonist	First line in suspected central etiology	Nephrotoxicity, over sedation, ataxia and confusion
Gabapentin	300–600 mg/day	Neuronal voltage gated calcium channel agonist Modulates diaphragm/ Inspiratory muscle	No RCTs	Sleepiness, Unsteadiness
Pregabalin	75–150 mg/day	Neuronal voltage gated calcium channel agonist Modulates diaphragm/ Inspiratory muscle	No RCTs	Sleepiness, dizziness, Dry mouth
Second line				
Metoclopramide	30 mg/day	Stimulation of gastric motility, dopamine antagonist	May be tried as first line in suspected peripheral etiology	Diarrhoea, Extrapyramidal side effects
Domperidone	30 mg/day	Block dopamine receptors Fasten gastrointestinal peristalsis	No large trials to support	Diarrhoea, dry mouth
Third line				
Chlorpromazine	25–50 mg/day	Dopamine antagonist	Only US FDA approved pharmacologic for hiccups, efficacy based on historical case studies only	Dry mouth, dizziness, constipation
Others				
Carbamazepine	25–50 mg/day	-	-	Dizziness, drowsiness, ataxia, vomiting
Valproate	20 mg/kg/day	-	-	Headache, Insomnia, somnolence, tremor, blurred vision, nausea, weight gain, rash, pancreatitis
Phenytoin	100 mg/day	-	-	Rash, sedation, neuropathy, gum hypertrophy, locomotor dysfunction, hyperkalaemia, megaloblastic anaemia
Amitriptyline	25–100 mg/day	-	-	Orthostatic hypotension, dizziness, constipation, sedation

PPI: Proton pump inhibitor, bid: Two times a day, GABA: Gamma amino butyric acid, Ca: Calcium, RCT: Randomized controlled trial



Algorithm 2: Treatment algorithm. GI: Gastrointestinal, CT: Computerised tomography, MRI: Magnetic resonance imaging, PPI: Proton pump inhibitor, TDS: Three times a day, QID: Four times a day

doesn't respond to or is intolerant to oral medication then IM or IV route can be tried. It should be used as second- or third-line therapy in persistent hiccups.[6,43]

Other drugs that are found effective in abolishing intractable hiccups are certain anticonvulsants such as phenytoin, valproic acid, carbamazepine, antidepressants like amitriptyline, CNS stimulants like marijuana, methylphenidate, and oral viscous lidocaine (2%) solution.

These are shown effective in certain case reports haloperidol, midazolam, nifedipine, nimodipine, and orphenadrine have

been tried in hiccups with evidence by small case studies and case reports.[14,42,44]

The use of combination therapy for hiccups lacks sufficient level of evidence. Few case reports mention combinations of olanzapine with baclofen, lansoprazole, and clonazepam, with dimenhydrinate[14] A case series showed the combination of baclofen, omeprazole, and cisapride improved or cessation of hiccups in nine of 15 patients.

Duration of pharmacotherapy

Duration of treatment depends upon underlying etiology but most drug treatments are enough for 5–10 days (with the exception of PPIs, which are continued for 3–4 weeks). In case of relief from hiccups, treatment can usually be stopped the day after cessation of hiccups. In some patients receiving palliative care like terminal malignancy, an indefinite duration of pharmacotherapy may be warranted. Here, we have proposed an algorithm for the management of hiccups [Algorithm 2].

CONCLUSION

Hiccups are challenging for physicians. Most hiccups are self-limited. Identifying the cause is important and should be treated accordingly. The pathogenesis of persistent hiccups is complex and diverse. It is mostly GI related, followed by CNS or post-operative etiologies. Empiric PPI therapy is recommended in GI-related hiccups. If initial medication is ineffective, it is reasonable to switch therapies after 3–4 weeks of use or trial of combination therapy if possible. Acute hiccups usually respond to physical therapies. Most commonly used maneuver is breath holding. For hiccups refractory to initial pharmacotherapies, it is reasonable to consider complementary and alternative medicine treatments such as acupuncture and hypnosis. Eventually hiccups unrelieved by physical maneuvers or pharmacotherapy, interventions that target the diaphragm like vagus nerve or phrenic nerve can be tried. After ruling out organic causes and before invasive therapies, it is prudent to treat psychogenic causes with a trial of anti-psychotic or anxiolytic medications. Future studies are needed for head-to-head drug comparison in hiccups treatment. Large patients control studies are required for alternative therapies for hiccups to include them at right place in management plan of hiccups. Randomized trial to compare hypnosis and acupuncture with pharmacotherapies will be interesting if something comes up useful.

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