



E-ISSN: 2788-9254
P-ISSN: 2788-9246
IJPSDA 2024; 4(1): 01-06
www.pharmacyjournal.info
Received: 03-05-2024
Accepted: 07-06-2024

Yash Srivastav
Assistant Professor, Azad
Institute of Pharmacy &
Research, Lucknow, Uttar
Pradesh, India

Nutan Shrivastava
City Women's College,
Jankipuram, Lucknow, Uttar
Pradesh, India

Km. Anjali
Veer Bahadur Singh
Purvanchal University,
Jaunpur, Uttar Pradesh, India

Aditya Srivastav
Institute of Pharmacy
Bundelkhand University,
Kanpur Road Jhansi, Uttar
Pradesh, India

Correspondence
Yash Srivastav
Assistant Professor, Azad
Institute of Pharmacy &
Research, Lucknow, Uttar
Pradesh, India

Hiccups (Singultus) a perspective analysis schematic overview and its prevention and treatment

Yash Srivastav, Nutan Shrivastava, Km. Anjali and Aditya Srivastav

DOI: <https://doi.org/10.22271/27889246.2024.v4.i2a.90>

Abstract

Involuntary synchronous contractions of the diaphragm and intercostal muscles that result in abrupt inspiration are known as Hiccups (singultus). The Latin word "singult," which means "to catch one's breath while sobbing," is the source of the medical name singultus. The diaphragm and intercostal muscles suddenly and involuntarily contract, causing hiccups. This produces a distinctive sound and causes the glottis to close virtually simultaneously. Hiccups can be categorized as transient, persistent, or recurrent based on how long they stay. Transient hiccups are short-lived episodes lasting seconds or minutes, whereas persistent bouts last more than 48 hours and are frequently repeated. While attempting to weigh a hog before butchering it in 1922, Charles Osborne (1894-1991) of Anthon, Iowa, in the United States, began suffering from seizures. He searched for a remedy but was unable to stop, thus he hiccuped for 68 years, till February 1990. Self-care: While there is currently no known cure for hiccups, it may be beneficial to try holding your breath, breathing into a paper bag, drinking cold water, or gargling with ice water. Medical attention: Consult a physician if your hiccups last longer than two days. Have trouble eating, sleeping, or breathing. In this article, we assess the current state, possible therapies, and underlying causes of hiccups.

Keywords: Hiccups, etiology, pathophysiology, diagnosis, treatment

Introduction

Hiccups are involuntary, recurring spasms or abrupt diaphragmatic movements. The muscle that divides your chest from your stomach plays a vital function in breathing: the diaphragm—your vocal cords abruptly close during a diaphragm spasm, creating a "hic" sound. Acute hiccups endure shorter than 48 hours, persistent hiccups last more than two days, and intractable hiccups last more than a month. There are numerous reasons why they could occur. Specifically, digestive issues such as gastroesophageal reflux frequently result in hiccups. Medication side effects, cardiovascular problems, central nervous system problems, illnesses of the ears, nose, and throat, psychogenic disorders, or metabolic disorders are some more explanations. This exercise examines the range of hiccups, from minor to severe, describes their causes, and provides treatment suggestions depending on clinical presentation. Most people will, at some point in their lives, experience the regular occurrence of hiccups. Singultus is the medical term, derived from the Latin 'singult' which means "to catch one's breath while "sobbing." The diaphragm and intercostal muscles suddenly and involuntarily contract, causing hiccups. The contractions are followed by an abrupt glottis closure, which results in the distinctive "hic" sound. These can happen to children, adults, babies, and unborn children. They have no physiological function in adulthood. It is thought that they could be involved in training respiratory muscles in utero ^[1]. Acute hiccups can be annoying and uncomfortable for a short while, but persistent and intractable hiccups can seriously impair quality of life as they can cause difficulties with speaking, eating, sleeping, and social interactions. They can also be an indication of major medical pathology ^[2]. Hiccups are the result of diaphragm and, often, intercostal muscle contractions that happen on their own. Since Bailey's 1943 proposal, it has been largely acknowledged that a "reflex arc" consisting of afferent, central, and efferent components causes hiccups. The sympathetic nerve fibres (thoracic outflow T6-T12), phrenic nerves, or the vagus nerve transport the afferent impulse. The brainstem in the medulla oblongata close to the respiratory centre, the reticular formation, the hypothalamus, and the upper spinal cord (C3–C5) appear to be regions of the CNS implicated in the hiccup response. This central mechanism can be modulated by dopaminergic and gamma-aminobutyric acid (GABA-ergic) neurotransmitters.

A unilateral or, less frequently, bilateral diaphragmatic contraction has been observed as a reflex carried via the phrenic nerve's efferent response. The intercostal muscles contract as a result of the activation of the accessory nerves. The recurrent laryngeal branch of the vagus nerve reflexively closes the glottis to complete this stereotyped series of actions. Without glottal closure, hiccups induce substantial hyperventilation in patients with tracheotomies, making it a crucial protective reaction [3]. Individuals experiencing uncontrollable and continuous hiccups may visit their primary care physician, the emergency department, urgent care centres, or health clinics for assessment. Based on the patient's history and physical examination, providers in these settings may begin treatment. Obtaining a complete history and physical examination is necessary to exclude more severe underlying causes. Any area that raises concerns should be brought to the attention of the relevant professional. While hiccups may seem unimportant, triage nurses and other healthcare professionals must understand that every complaint warrants a complete history and assessment. If the patient is not a good candidate for outpatient therapy or has not responded well to it, consultation and referrals are warranted if there is an obvious or suspected underlying disease. Patients may need to be referred to gastroenterology for an endoscopy, as well as otolaryngology, neurology, or pulmonology if their initial outpatient therapy fails and there is no obvious reason why. Rarely, unmanageable instances may require a referral to anesthesiologists for a nerve block. A common complaint from cancer patients receiving hospice care is tic tacs. Since recurring hiccups may hurt the quality of life, palliative care physicians and nurses should create treatment plans to address these complaints. Oftentimes, hiccups are harmless and self-limiting. In addition to being reassured, patients experiencing acute hiccups should be encouraged to attempt the aforementioned physical techniques. Treatment for reflux may alleviate intractable and recurrent hiccups in healthy individuals without a clear reason. Appropriate initial actions include patient education and therapies targeted at enhancing gastrointestinal motility and reflux. The provider ought to offer advice regarding the possibility of any problems with quality of life [4].

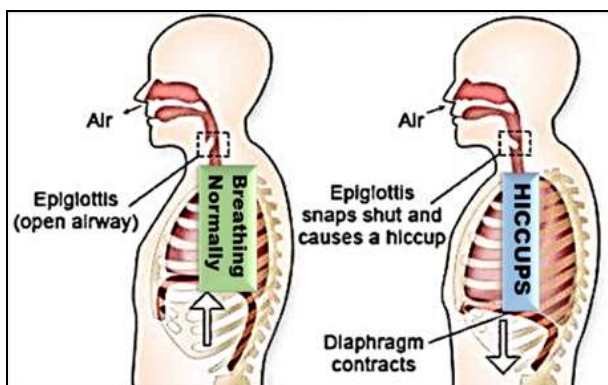


Fig 1: A diagrammatic illustration of hiccups and normal breathing

Epidemiology and History

Every age group, from infants to the elderly, experiences tic-tacs. It is uncertain how common hiccups are in the community, and there don't seem to be any ethnic or geographic variations in their frequency or prevalence. According to reports, 4,000 admissions for hiccups are

thought to occur each year in the United States. An odds ratio of 2.4 indicates that older males and those with higher weight and height are more likely to experience intractable hiccups. The incidence of persistent hiccups is higher in patients with certain disorders, especially those with central nervous system disorders such as Parkinson's Disease, and advanced cancer where the incidence may be as high as 4-9%, and 8-10% in those with gastroesophageal reflux disease (GERD) [5-9]. Assessing a patient who has hiccups requires a detailed review of their medical history. Inquire about any trigger events, such as heavy meals, excitement, or psychological tension. Find out about any related symptoms, such as weight loss, coughing, reflux, and stomach pain. Inquire about any neurological symptoms that could point to Parkinson's disease, multiple sclerosis, or a medullary stroke. Though rare, tic tacs during sleep can be caused by pulmonary, neurological, or oesophageal problems; they rule out a psychogenic explanation. Inquire about chemotherapy, recent surgery, and known malignancy. A thorough assessment of all prescribed drugs may reveal a probable cause; if stopping the problematic drug results in appreciable alleviation, causality is established. When hiccups are severe and chronic, it's best to look into organic causes. A complete evaluation by HEENT specialists may identify conditions including goitres, tonsillitis, pharyngitis, lumps, hair or the foreign body pressing against the tympanic membrane, and more. To rule out thoracic causes like pneumonia or empyema, listen to the lung sounds. To rule out blockage, volvulus, pancreatitis, hepatitis, or mass, palpate the abdomen for any soreness or mass. A thorough neurological examination may reveal CNS pathology, including tumours and strokes, albeit hiccups are not usually the sole symptom to appear [10].

Etiology

The duration of hiccups is used to categorize them. Less than 48 hours pass between acute hiccups, persistent hiccups last more than two days, and intractable hiccups last more than a month. The majority of studies have been on chronic and intractable hiccups because acute hiccups are self-limited and typically go unnoticed. Hiccups can have several origins, such as organic, psychogenic, idiopathic, or drug-induced ones. Uncontrollably recurring hiccups could indicate a more serious underlying cause. Acute hiccups are most commonly connected with digestive processes, including gastroesophageal reflux disease (GERD) and related hiatal hernias. It has been claimed that up to 10% of GERD patients get hiccups. Common correlations include stomach distension brought on by heavy meals, fizzy drinks, spicy foods, and alcohol. Up to one in four patients with oesophageal tumours may exhibit chronic hiccups. Similarly, the hiccup reflex can be brought on by excessive excitement or anxiety, particularly if it is accompanied by hyperventilation or air swallowing (like during laughing fits). Alcohol in particular is linked to hiccups when using many medicines. Hiccups and certain medications, such as benzodiazepines, have an inverse and dose-dependent connection. Benzodiazepines are correlated with the development of hiccups at low doses. They could help treat hiccups at greater doses. Hiccups have been strongly linked to certain glucocorticoids and chemotherapy drugs. Patients receiving both dexamethasone and cisplatin experience hiccups in about 42% of cases. Alpha-methyl dopa, inhalation anaesthetics, and some chemotherapy drugs are

other drugs linked to hiccups [11-14]. There are several accounts of chronic and uncontrollable hiccups caused by a wide range of conditions, such as cardiovascular disorders: atrial fibrillation, myocardial infarction, pericarditis, temporal arteritis, thoracic or abdominal aortic aneurysm, catheter ablation of atrial fibrillation, etc. Aneurysms (particularly posterior inferior cerebellar artery), encephalitis, lateral medullary syndrome, meningitis, multiple sclerosis, neuromyelitis optica, neoplasms (brain stem tumour, Astrocytoma), Parkinson's disease, seizures, stroke, syringomyelia, and vascular malformations (cavernoma) are among the disorders of the central nervous system (CNS). Drugs include alpha-methyl dopa, azithromycin, aripiprazole, benzodiazepines (midazolam, diazepam), chemotherapeutics (etoposide, cisplatin, carboplatin, ethanol, levofolinate, oxaliplatin), ethanol, donepezil, levodopa, methohexital, morphine, pergolide, piribedil, sulfonamides, and tramadol. ENT diseases include a cough, goitre, laryngitis, neck cysts, neoplasms, pharyngitis, and irritation of the tympanic membrane by foreign bodies (hair, for example). Infectious diseases include neurosyphilis, tuberculosis, influenza, herpes simplex, herpes zoster, and neurosyphilis. Asthma, bronchitis, diaphragmatic tumour or hernia, empyema, lymphadenopathy, mediastinitis, neoplasms, pleuritis, pneumonia, and pulmonary embolus are examples of intrathoracic illnesses. Hypocapnia, hypocalcemia, hypokalemia, hyponatremia, diabetes mellitus, and uremia are examples of metabolic/endocrine illnesses. Excitation, hyperventilation, malingering, somatization, and stress are examples of psychogenic disorders. Surgery: tracheostomy, post-operative bronchoscopy, stomach insufflation during endoscopy, anaesthetic drugs (barbiturates, bupivacaine epidural, isoflurane, methohexital, propofol), sedation during endoscopy (20% occurrence) [15-20].

Pathophysiology

It is believed that a complicated reflex arc made up of three primary parts causes hiccups. Any illness that affects one of these channels can cause hiccups. The vagus nerve, phrenic nerve, and peripheral sympathetic nerves that supply the viscera make up the afferent limb in the first place. Second, the interaction between different midbrain and brainstem structures-like the medulla oblongata and reticular formation, chemoreceptors in the periaqueductal grey, glossopharyngeal and phrenic nerve nuclei, solitary and ambiguous nuclei, hypothalamus, temporal lobes, and upper spinal cord at levels C3 to 5-is probably going to be involved in the CPU. The central neurotransmitters serotonin, gamma-aminobutyric acid (GABA), and dopamine are implicated in this reaction. Third, the phrenic nerve, which supplies the diaphragm, and the accessory nerves, which feed the intercostal muscles, make up the efferent part of the reflex. Hiccups typically recur four to sixty times a minute, depending on the person. The left hemidiaphragm is more affected than the right during a diaphragmatic spasm, which is frequently unilateral. The recurrent laryngeal nerve is activated to complete the reflex after the diaphragmatic spasm, which results in the closure of the glottis. As a kind of diaphragmatic myoclonus, hiccups become chronic because of overactivity in the lone medulla nucleus. The glottis would not close, causing hyperventilation. Elevations in partial pressure of carbon dioxide (PCO₂), vagal movements, GABA-ergic drugs (like

baclofen, and gabapentin), and dopamine agonists (like amantadine) or antagonists (like chlorpromazine, haloperidol, and metoclopramide) can all prevent tic episodes [21-24].

Diagnosis

The length of hiccups, history, and physical exam results are the best criteria for directing additional imaging or therapies. Brain imaging using computerized tomography (CT) or magnetic resonance imaging (MRI) may reveal causes such as stroke, multiple sclerosis, tumour, syringomyelia, neuromyelitis optica, aneurysm, or vascular malformation for persistent or uncontrollable hiccups linked to neurologic symptoms or signs. A comprehensive evaluation should be conducted to determine a treatable cause of chronic and intractable hiccups, as they are usually benign and do not necessitate a workup. It makes sense to do lab work to evaluate electrolyte imbalances or to rule out infectious or malignant processes that were not detected during the physical examination and history. Tests in the laboratory for electrolytes, calcium, creatinine, lipase, blood urea nitrogen (BUN), and liver function can be helpful. A chest radiograph can help diagnose intrathoracic conditions such as pneumonia, empyema, diaphragmatic hernia, adenopathy, or aortic disease that could be causing the hiccups. Reviewing blood gases is crucial for any ventilated patient experiencing hiccups. In patients on ventilation, hiccups can result in hemodynamic alterations, significant respiratory disturbances, and ventilator desynchronization [25-27].

Complications with Hiccups

While persistent and intractable hiccups can have a significant negative impact on quality of life due to decreased ability to tolerate oral intake, which can result in dehydration, malnutrition, fatigue, and weight loss as well as insomnia, despair, depression, and exhaustion, acute hiccups cause temporary discomfort, GERD, emotional disturbance, and rarely aspiration. Patients in the neuro ICU on intubation who experience hiccups may face problems due to hemodynamic shifts and ventilatory desynchronization. A tic tac can cause problems during surgery or jeopardize the healing of abdominal or thoracic wounds that were previously closed. Bradycardia, carotid dissection, barotrauma (pneumothorax, pneumomediastinum) and hypotension (low venous return) are all possible outcomes of forceful hiccups [28].

Treatment of hiccup disorders

Monitoring whether the patient is taking a drug known to cause hiccups and determining whether hiccups are related to GERD are crucial first stages in treating chronic and intractable hiccups. Medicine-induced hiccups can be avoided by stopping the problematic medicine or switching to an alternative (methylprednisolone instead of dexamethasone, for example). An early therapeutic trial of antacids, antihistamines (like famotidine) or proton pump inhibitors (like omeprazole) may be beneficial, and this method has been recommended as a first-line therapy since up to 80% of instances of persistent hiccups are linked to GERD [29-31]. Some easy physical techniques can stop hiccups in their acute phase, according to anecdotal evidence. A section of the hiccup reflex arc is the target of most techniques. As PCO₂ rises, hiccup frequency

decreases, therefore blowing into a paper bag, holding your breath, and performing Valsalva maneuvers may be helpful. In the supra-supramaximal inspiration technique, the subject exhales fully, inhales deeply, and holds the breath for 10 seconds. Then, without exhaling, the subject inhales twice more, holding the breath for 5 seconds each time. Additional methods include applying pressure to the carotid artery, the eyeballs, or both external auditory canals; pulling on the tongue; sipping vinegar; swallowing sugar; stimulating the uvula or posterior nasopharynx (with smelling salts or nasal vinegar); performing the Valsalva manoeuvre; gargling, gagging, or even self-induced vomiting. There have been reports of other strange methods such as digital rectal massage and sexual stimulation. Suboccipital release and osteopathic/chiropractic manipulation procedures have been reported. In the acute period, all of these methods seem to work substantially better. Treatment during the persistent phase is typically more challenging and complex (32–39). The majority of research has assessed pharmacotherapies that target one or more reflex arc components during the persistent phase. Targeting neurotransmitters, pharmacotherapy can be divided into treatments that act on the central and peripheral nervous systems, but some affect both. The neurotransmitters serotonin, dopamine, and GABA are involved in central processing. Acetylcholine, histamine, epinephrine, and norepinephrine are examples of peripheral neurotransmitters. Historically, the only medication for hiccups that has been approved by the US Food and Medicine Administration (FDA) is chlorpromazine, which continues to be the medicine of choice for persistent hiccups. Numerous central and peripheral neurotransmitter sites, such as dopamine, serotonin, histamine receptors, alpha-adrenergic receptors, and muscarinic receptors, are antagonistically affected by chlorpromazine. For certain patients, the drug's numerous sites of action may result in serious side effects. Different common antipsychotics, including risperidone or haloperidol, have also been tested, with differing degrees of efficacy. Frequently, patients may find the adverse effects of standard antipsychotic medications intolerable. The most often researched medications for intractable or chronic hiccups are gabapentin, baclofen, and metoclopramide, which are GABA agonists. These three medications have less side effects than standard antipsychotics. Second-line therapies such as metoclopramide, gabapentin, or baclofen are suitable if a comprehensive exam fails to reveal the cause. Metoclopramide has been successfully used to treat hiccups caused by cancer, stroke, and brain tumours. It works peripherally by increasing stomach motility and centrally as a dopamine antagonist. Intractable hiccups in stroke patients and idiopathic causes without gastric reflux illness have been effectively treated with baclofen, which works by reducing neuroexcitation and promoting muscular relaxation. Similarly, by binding voltage-gated calcium channels and reducing the release of excitatory neurotransmitters, gabapentin—which shares structural similarities with decreases neuroexcitation. Gabapentin is 66–88% effective in treating brainstem stroke and cancer patients in one case series. Anecdotal reports suggest that several medications, including amantadine, amitriptyline, antipsychotic agents (haloperidol, risperidone, olanzapine), atropine, benzonatate, carvedilol, glucagon, ketamine, midazolam, nifedipine, nimodipine, orphenadrine, and valproic acid, are effective in treating persistent hiccups.

Various injectable drugs, such as atropine, ephedrine, dexmedetomidine, ketamine, and lidocaine, have been used to treat intraoperative hiccups. Other distribution techniques for local anaesthetics include subcutaneous infusions, external auditory canal lidocaine gel, and oral viscous lidocaine. Acupuncture, positive pressure ventilation, vagus nerve stimulators, and stellate or phrenic nerve block are examples of more intrusive management methods. Acupuncture has shown encouraging effects in small trials treating intractable hiccups in stroke and cancer patients. For some patients who are too ill or elderly to get medication or more invasive procedures, it might be a feasible alternative given the relatively low complication rate and potential benefit. According to certain case studies, positive pressure ventilation combined with elective intubation can be effective. It's critical to confirm that both hemi-diaphragms are working before severing or inhibiting the phrenic nerve to relieve symptoms [40, 41, 50, 42–49].

Discussion and Conclusion

A review of hiccups, including their many origins, epidemiology, and alternative therapies, is included in the first section of our review articles. While drugs and other therapies can help treat hiccups, our research suggests otherwise. Hiccups require additional randomized controlled trials to be addressed. We would like to undertake an initial study on Hiccups in the future. In our nation or state, future counseling-based research will evaluate patients' physical and mental health and provide more precise information on hiccups and their treatment, thanks to the collaboration of our colleagues.

Ethical Statement

Maintain a high standard of conduct and tell the truth in all of our contacts and work-related activities. Let us be truthful in our speech and behaviour.

Acknowledgement

The authors would like to thank, Azad Institute of Pharmacy & Research (AIPR), Lucknow, U.P, India, Lucknow, Uttar Pradesh, India for extending their facilities.

Conflict of Interest

The authors attest that they are free of any known financial or personal conflicts of interest that would taint the findings of this study.

Informed Consent

Using websites, review articles, and other sources to produce research content.

References

1. Kahrilas PJ, Shi G. Why do we hiccup? *Gut*. 1997;41(5):712-713.
2. Samuels M. Hiccup. *Canadian Medical Association Journal*. 1952;67:315-322.
3. Steger M, Schneemann M, Fox M. Systemic review: The pathogenesis and pharmacological treatment of hiccups. *Alimentary Pharmacology & Therapeutics*. 2015;42(9):1037-1050.
4. Porzio G, Aielli F, Verna L, Aloisi P, Galletti B, Ficorella C. Gabapentin in the treatment of hiccups in patients with advanced cancer: A 5-year experience. *Clinical Neuropharmacology*. 2010 Jul;33(4):179-180.

5. Rey E, Elola-Olaso CM, Rodríguez-Artalejo F, Locke GR 3rd, Díaz-Rubio M. Prevalence of atypical symptoms and their association with typical symptoms of gastroesophageal reflux in Spain. *European Journal of Gastroenterology & Hepatology*. 2006 Sep;18(9):969-975.
6. Lee GW, Kim RB, Go SI, Cho HS, Lee SJ, Hui D, *et al*. Gender differences in hiccup patients: Analysis of published case reports and case-control studies. *Journal of Pain and Symptom Management*. 2016 Feb;51(2):278-283.
7. Hosoya R, Uesawa Y, Ishii-Nozawa R, Kagaya H. Analysis of factors associated with hiccups based on the Japanese Adverse Drug Event Report database. *PLoS ONE*, 2017, 12(2).
8. Souadjian JV, Cain JC. Intractable hiccup: Etiologic factors in 220 cases. *Postgraduate Medicine*. 1968 Feb;43(2):72-77.
9. Calsina-Berna A, García-Gómez G, González-Barboteo J, Porta-Sales J. Treatment of chronic hiccups in cancer patients: A systematic review. *Journal of Palliative Medicine*. 2012 Oct;15(10):1142-1150.
10. Cole JA, Plewa MC. Singultus. [Updated 2023 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK538225/>.
11. de Hoyos A, Esparza EA, Cervantes-Sodi M. Non-erosive reflux disease manifested exclusively by protracted hiccups. *Journal of Neurogastroenterology and Motility*. 2010 Oct;16(4):424-427.
12. García Callejo FJ, Redondo Martínez J, Pérez Carbonell T, Monzó Gandía R, Martínez Beneyto MP, Rincón Piedrahita I. Hiccups: Attitude in Otorhinolaryngology towards consulting patients. A diagnostic and therapeutic approach. *Acta Otorrinolaringologica Española*. 2017;68(2):98-105.
13. Khorakiwala T, Arain R, Mulsow J, Walsh TN. Hiccups: An unrecognized symptom of esophageal cancer? *The American Journal of Gastroenterology*. 2008;103:801.
14. Steger M, Schneemann M, Fox M. Systemic review: The pathogenesis and pharmacological treatment of hiccups. *Alimentary Pharmacology & Therapeutics*. 2015 Nov;42(9):1037-1050.
15. Liu CC, Lu CY, Changchien CF, Liu PH, Perng DS. Sedation-associated hiccups in adults undergoing gastrointestinal endoscopy and colonoscopy. *World Journal of Gastroenterology*. 2012 Jul;18(27):3595-3601.
16. Hansen BJ, Rosenberg J. Persistent postoperative hiccups: A review. *Acta Anaesthesiologica Scandinavica*. 1993 Oct;37(7):643-646.
17. Mehra A, Subodh BN, Sarkar S. Psychogenic hiccup in children and adolescents: A case series. *Journal of Family Medicine and Primary Care*. 2014;3:161-163.
18. Pooran N, Lee D, Sideridis K. Protracted hiccups due to severe erosive esophagitis: A case series. *Journal of Clinical Gastroenterology*. 2006 Mar;40(3):183-185.
19. Zingale A, Chiaramonte I, Consoli V, Albanese V. Distal posterior inferior cerebellar artery saccular and giant aneurysms: Report of two new cases and a comprehensive review of the surgically-treated cases. *Journal of Neurosurgical Sciences*. 1994 Jun;38(2):93-104.
20. Wang KC, Lee CL, Chen SY, Lin KH, Tsai CP. Prominent brainstem symptoms/signs in patients with neuromyelitis optica in a Taiwanese population. *Journal of Clinical Neuroscience*. 2011 Sep;18(9):1197-1200.
21. al Deeb SM, Sharif H, Al Moutaery K, Biary N. Intractable hiccup induced by brainstem lesion. *Journal of the Neurological Sciences*. 1991 Jun;103(2):144-150.
22. Moretti R, Torre P, Antonello RM, Ukmar M, Cazzato G, Bava A. Gabapentin as a drug therapy of intractable hiccup because of vascular lesion: A three-year follow up. *The Neurologist*. 2004 Mar;10(2):102-106.
23. Polito NB, Fellows SE. Pharmacologic interventions for intractable and persistent hiccups: A systematic review. *Journal of Emergency Medicine*. 2017 Oct;53(4):540-549.
24. Nausheen F, Mohsin H, Lakhan SE. Neurotransmitters in hiccups. *SpringerPlus*. 2016;5(1):1357.
25. Kolodzik PW, Eilers MA. Hiccups (singultus): Review and approach to management. *Annals of Emergency Medicine*. 1991 May;20(5):565-573.
26. Kulkarni GB, Kallollimath P, Subasree R, Veerendrakumar M. Intractable vomiting and hiccups as the presenting symptom of neuromyelitis optica. *Annals of Indian Academy of Neurology*. 2014;17:117-119.
27. Howard RS, Radcliffe J, Hirsch NP. General medical care on the neuromedical intensive care unit. *Journal of Neurology, Neurosurgery & Psychiatry*, 2003 Sep, 74 3(3).
28. Rousseau P. Hiccups. *Southern Medical Journal*. 1995 Feb;88(2):175-181.
29. Petroianu G, Hein G, Petroianu A, Bergler W, Rüfer R. Idiopathic chronic hiccup: Combination therapy with cisapride, omeprazole, and baclofen. *Clinical Therapeutics*. 1997;19(5):1031-1038.
30. Cabane J, Bizec JL, Derenne JP. [A diseased esophagus is frequently the cause of chronic hiccup. A prospective study of 184 cases]. *La Presse Médicale*, 2010 Jun, 39(6).
31. Lee GW, Oh SY, Kang MH, Kang JH, Park SH, Hwang IG, *et al*. Treatment of dexamethasone-induced hiccup in chemotherapy patients by methylprednisolone rotation. *The Oncologist*. 2013;18(11):1229-1234.
32. Kwan CS, Worriw CC, Kovelman I, Kuklinski JM. Using suboccipital release to control singultus: A unique, safe, and effective treatment. *The American Journal of Emergency Medicine*. 2012 Mar;30(3):514.e5-7.
33. Seidel B, Desipio GB. Use of osteopathic manipulative treatment to manage recurrent bouts of singultus. *The Journal of the American Osteopathic Association*. 2014 Aug;114(8):660-664.
34. Fesmire FM. Termination of intractable hiccups with digital rectal massage. *Annals of Emergency Medicine*. 1988;17(8):872.
35. Petroianu GA. Treatment of singultus by sexual stimulation: Who was George T Dexter, MD (c1812-?)? *Journal of Medical Biography*. 2016 May;24(2):252-261.
36. Petroianu GA. Treatment of hiccup by vagal maneuvers. *Journal of the History of the Neurosciences*. 2015;24(2):123-136.

37. Petroianu GA. Treatment of singultus by traction on the tongue: an eponym revised. *Journal of the History of the Neurosciences*. 2013;22(2):183-190.
38. Morris LG, Marti JL, Ziff DJ. Termination of idiopathic persistent singultus (hiccup) with supra-supramaximal inspiration. *The Journal of Emergency Medicine*. 2004;27(4):416-417.
39. Davis JN. An experimental study of hiccup. *Brain*. 1970;93(4):851-872.
40. Byun SH, Jeon YH. Treatment of idiopathic persistent hiccups with positive pressure ventilation: A case report-. *The Korean Journal of Pain*. 2012;25(2):105-107.
41. Ge AXY, Ryan ME, Giaccone G, Hughes MS, Pavletic SZ. Acupuncture treatment for persistent hiccups in patients with cancer. *Journal of Alternative and Complementary Medicine*. 2010 Jul;16(7):811-816.
42. Yue J, Liu M, Li J, Wang Y, Hung ES, Tong X, *et al*. Acupuncture for the treatment of hiccups following stroke: a systematic review and meta-analysis. *Acupuncture in Medicine*. 2017 Mar;35(1):2-8.
43. Choi TY, Lee MS, Ernst E. Acupuncture for cancer patients suffering from hiccups: A systematic review and meta-analysis. *Complementary Therapies in Medicine*. 2012 Dec;20(6):447-455.
44. Moretto EN, Wee B, Wiffen PJ, Murchison AG. Interventions for treating persistent and intractable hiccups in adults. *The Cochrane Database of Systematic Reviews*, 2013 Jan, 2013(1).
45. Grewal SS, Adams AC, Van Gompel JJ. Vagal nerve stimulation for intractable hiccups is not a panacea: A case report and review of the literature. *International Journal of Neuroscience*. 2018 Dec;128(12):1114-1117.
46. Lee AR, Cho YW, Lee JM, Shin YJ, Han IS, Lee HK. Treatment of persistent postoperative hiccups with stellate ganglion block: Three case reports. *Medicine (Baltimore)*, 2018 Nov, 97(48).
47. Kaneishi K, Kawabata M. Continuous subcutaneous infusion of lidocaine for persistent hiccup in advanced cancer. *Palliative Medicine*. 2013 Mar;27(3):284-245.
48. Thomas RH, Thomas NJP. Miracle hiccough cure gets the attention it deserves. *BMJ (Clinical Research Ed.)*. 2006;333(7571):1222.
49. Neuhaus T, Ko YD, Stier S. Successful treatment of intractable hiccups by oral application of lidocaine. *Supportive Care in Cancer*. 2012 Nov;20(11):3009-3011.
50. Bahadoori A, Shafa A, Ayoub T. Comparison of the effects of ephedrine and lidocaine in treatment of intraoperative hiccups in gynecologic surgery under sedation. *Advanced Biomedical Research*. 2018;7:146.