Current Oncology Reports (2019) 21: 113
https://doi.org/10.1007/s11912-019-0857-4

PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

Perspectives on the Medical, Quality of Life, and Economic Consequences of Hiccups

Katharine Hendrix[1] · David Wilson[2] · MJ Kievman[3] · Aminah Jatoi[4]

Published online: 19 December 2019

Abstract

Purpose of Review Singultus or hiccups (HU) is a common, usually temporary, event. Its potentially serious consequences are often overlooked. This review explores published evidence describing HU burden (clinical, economic, and quality of life [QoL] consequences) across patient populations.

Recent Findings Literature review identified 81 articles (including 57 individual case reports). We extracted relevant information to better understand the burden of HU and to identify knowledge gaps for future study.

Summary HU are physiologic events that can complicate existing medical conditions and treatments regardless of duration. Relatively short episodes can have devastating consequences in patients who have pre-existing conditions. HU appear to impact physical and psychological health, diminish QoL, increase healthcare resource use, and increase costs. A better understanding of HU burden is needed.

Keywords Hiccups · Hiccoughs · Singultus · Burden of illness · Morbidity

Introduction

In the year 1647, Lupton first described hiccups (HU), otherwise known as singultus. Now, almost 400 years later, this common physiological event remains poorly understood [1]. Hiccups consist of repeated and involuntary contractions of the diaphragm and inter-costal muscles, causing rapid inspiration that is immediately followed by glottic adduction. The coordination of these events produces the signature "hic" sound [2]. The motor patterns underlying hiccups originate in the brainstem respiratory network and are tuned by the myriad of sensory afferents that converge on this network [3–5]. Despite the ubiquity of hiccups, there is a paucity of in-depth understanding of the driving mechanisms and evolutionary origin of this common malady [6, 7•, 8].

This article is part of the Topical Collection on *Palliative Medicine*

✉ David Wilson
Dwilson96@gmail.com

[1] Medical University of South Carolina, Charleston, SC, USA

[2] Meter Health, Inc., 197 Spring St., Arlington, MA 02476, USA

[3] Meter Health, Inc., Boston, MA, USA

[4] Mayo Clinic, Rochester, MN, USA

For the generally healthy person, HU episodes do not require medical attention. However, at times, HU can be debilitating or medically dangerous. Indeed, herein lies the justification for this review that aims to examine the burden of HU defined as downstream clinical consequences, negative impacts on patient QoL, and presumed economic impacts. Although benign and self-limited in the vast majority, HU can lead to extreme fatigue, sleep deprivation, weight loss, depression, anxiety, aspiration, pneumonia, and diaphragmatic rupture [2, 3, 9–25].

Hiccup severity is often classified by duration. Three common categories are acute HU (≤ 48 h), persistent/protracted HU (48 h to 1 month), and intractable HU (> 1 month) [26]. Occasionally, a fourth category, chronic HU (7 days to 1 month), and a fifth category, incoercible/recurrent HU (> 2 months), are used [7•, 27]. These classifications point to potential gaps in HU management. Because episode duration alone does not accurately convey HU severity or burden, the mandate to find better therapeutic approaches becomes illusory.

Methods

We conducted a literature review using MEDLINE for English language articles published from 1952 to 2018 with

MeSH terms: hiccup, persistent hiccup, persistent hiccough, persistent singultus, intractable hiccup, intractable hiccough, and intractable singultus. Because recent studies that help define HU burden are sparse, this review spanned a broad timeframe to provide a single source of extant data. Bibliographies from gathered articles were further searched for citations that met the above criteria.

Single case reports were included. Articles that did not include primary clinical information were excluded. A decision was made not to focus on therapeutic treatment except when HU burden impacted use of healthcare resources and costs, as there are strong and relatively recent systematic literature reviews of HU treatments [28–30].

Results

A total of 81 articles were extracted. The majority ($N = 57$) were case reports with 47 being single case studies. No studies specifically assessed the overall HU burden (clinical, QoL, and economic consequences). However, six assessed some aspect of HU burden including clinical consequences and healthcare resource use in patients with psychogenic polydipsia; clinical consequences and treatment outcomes in otorhinolaryngology patients; clinical and QoL consequences in post-stroke patients undergoing inpatient rehabilitation; clinical and QoL consequences in advanced neuro-oncology patients receiving palliative care; clinical consequences in patients with neuromyelitis optica (NMO); and a specific clinical consequence (sleep disruption) in patients referred to a specialty HU clinic [7•, 23, 31–34].

Hiccups Epidemiology

Epidemiological findings were mostly from secondary observations and reporting. When authors did not clearly report an incidence or prevalence rate, we extracted and summarized incidence (risk of developing HU) from the number of newly developed cases in the study population and prevalence (likelihood of having HU) from the number of people with HU in the study population. While HU have been associated with over 100 etiologies, source data on incidence and prevalence was found in only 6 broad patient populations (Table 1) [35, 36].

Variability in HU incidence ranged from < 1 to > 80%. The lowest incidence (0.39%) was reported by a study of pharmaceutical clinical trial databases of patients receiving at least one of nine cancer chemotherapies [37]. The highest incidence (84.8%) was reported in a randomized controlled trial that assessed dexamethasone in cancer patients [38].

We only found HU prevalence information in two studies, both in gastroesophageal reflux disease (GER or GERD) [39, 40]. The study by Rey et al. is of note for its robust methodology. This population study was designed to estimate prevalence rates of atypical GER symptoms in a randomly selected sample of 2500 [40]. The study found an overall HU prevalence of 9% (95% CI; 7.9–10.2%) with rates as high as 18.8% (95% CI; 13.9–23.7%) among patients with frequent (minimum weekly) GER symptoms [40].

Risk Factors

A variety of demographic, clinical, and treatment characteristics are noted as HU risk factors. Three studies included in Table 1 analyzed multiple demographic and clinical risk factors [41, 46••, 47]. Gender was the only common significant risk factor, with males at greater risk in each study. In addition to gender, in chemotherapy patients taking cisplatin, Liaw et al. found significantly higher frequency of HU with higher doses of cisplatin ($p = 0.006$), absence of vomiting during chemotherapy ($p = 0.001$), and absence of nausea during chemotherapy ($p < 0.0001$) [41]. Liu et al. found that patients undergoing endoscopic examination who received premedication with buscopan had higher HU prevalence ($p = 0.066$) [47]. Hosoya et al. studied risk factors for chemotherapy-induced HU and found male gender (OR 72.69; $p = 0.0003$); symptoms of nausea and vomiting (OR 41.94; $p = 0.002$); and receiving dexamethasone (OR 4.55; $p = 0.0237$), cisplatin (OR 3.85; $p = 0.0044$), and etoposide (OR 3.72; $p = 0.0293$) were significant independent risk factors for HU [46••]. Height, weight, body surface area, "lung" as type of cancer, type of anticancer medication, and antiemetic drugs and dose were also significant risk factors in univariate analyses, but did not reach significance in the multivariate analysis [46••].

Gender is perhaps the most recognized risk factor for HU and was a noted risk factor in other studies reviewed (see subgroup reporting in Table 1). In all cases, HU risk was higher in males than females with one exception. A large study by Rey et al. in GER patients ($N = 2500$) found significantly more HU ($p < 0.05$) among women than men (10% females [$n = 1315$]; 7.9% males [1185]) [40]. Lee et al. investigated male predominance of HU in a systematic literature review [53]. This analysis of case reports/series of patients with HU only ($n = 864$) found that the proportion of men (81.9%) with HU was significantly higher than that of women ($p < 0.001$) [52]. Lee et al. also conducted a further meta-analysis of six studies with case controls and found that HU of non-CNS origin was significantly associated with male gender (OR 11.72; $p < 0.001$) but not HU of CNS origin (OR 1.74; $p = 0.072$) [52].

Clinical Consequences

It is striking that HU affected such a broad spectrum of patients in such a variety of detrimental ways. Across the

Table 1 Hiccups incidence and prevalence

Disease	Patients	Sample size	Incidence	Prevalence	Subgroups	Source
Cancer	Receiving cisplatin and dexamethasone chemotherapy (Taiwan)	277	41.02%		Male (52.4%) Female (4.6%); ($p < 0.0001$)	Liaw, 2005 [41]
Cancer	Receiving ≥1 of 9 chemotherapy agents from 1979-2001[a] (Japan)	41,215	0.39%		Male (0.7%) Female (0.03%); ($p < 0.0001$)	Takiguchi, 2002 [37]
Cancer	Bone marrow transplant with tunneled catheter placement (Turkey)	75	1.3%			Parlak, 2006 [42]
Cancer	Receiving home care for advanced cancer (Italy)	362	3.86%		-HU over 6 months $n = 8$ "occasional" $n = 5$ "persistent" $n = 1$ "continuous" -Higher incidence in men; ($p = 0.006$)	Mercadante, 2013 [43]
Cancer	Receiving dexamethasone chemotherapy[f] (Korea)	65	84.8% (in dexamethasone group) 62.5% (methylprednisolone)		-No women enrolled -Greater HU intensity with dexamethasone (NRS, 3.5 vs. 1.4; $p < 0.001$)	Go, 2017 [38]
Cancer	Receiving dexamethasone[b] chemotherapy (Canada)	60	25%		-77% of sample female -HU during 1 week chemo: 17% a little 8% quite a bit 0% a lot	Vardy, 2006 [44]
Cancer	Receiving cisplatin and palonosetron, aprepitant, and dexamethasone chemotherapy[g] (Taiwan)	69	26%		18% incidence in second round of chemotherapy	Yang, 2016 [45]
Cancer	Receiving chemotherapy April–December, 2014[i] (Japan)	292	16.4%		Male gender was an independent risk factor (OR 72.69)	Hosoya, 2018 [46••]
GER[c]	Randomly selected from the general population[d] (Spain)	2500		9%	Female 10.0% Male 7.9%; ($p < 0.05$)	Rey, 2006 [40]
GER[c]	Receiving proton pump inhibitors[h] (Italy)	266		5%	3% prevalence in erosive GER vs. 7% in non-erosive GER ($p = 0.129$)	Dore, 2007 [39]
GER[c]	Receiving endoscopy and colonoscopy with and without sedation (Taiwan)	425	20.5% (in sedated) 5.1% (in not sedated)		Majority developing HU are male ($p < 0.05$)	Liu, 2012 [47]
NMO[j]	Receiving treatment for NMO[j] or NMOSD[k] at 9 centers in 6 countries (France, United States, United Kingdom, Japan, Canada, Germany)	258	22%		Evaluated "intractable" HU defined as duration > 1 week	Kremer, 2014 [48]
NMO[j]	Receiving treatment for NMO[j] or at high risk for NMO[j] (Japan)	35	34%		15/35 (43%) had "intractable HU and nausea" (IHN); 12 HU patients were a subgroup[m] of 15 patients with IHN and excludes 3 who had nausea only without HU	Takahashi, 2008 [33]
Anesthesia	Receiving 1 of 3 anesthesia agents for surgery with LMA[l] insertion (United Kingdom)	150	2% (in propofol group) 4% (in lidocaine /thiopentone group) 14% (in midazolam /thiopentone group)			Bapat, 1996 [49]
Anesthesia	Receiving D & C[n] procedure using methohexitone with and without lidocaine pre-treatment (Israel)	200	6% (in lidocaine /methohexitone group) 16% (in methohexitone group)			Weksler, 1992 [50]
Renal failure		20	60%		Incidence is of "persistent" HU	Chang, 2000 [51]

Table 1 (continued)

Disease	Patients	Sample size	Incidence	Prevalence	Subgroups	Source
	Receiving dialysis and having star fruit-intoxication (Taiwan)					
Psychogenic polydipsia	Receiving treatment for symptomatic hyponatremia[e] (United States)	11	64%			Cronin, 1987 [31]
Stroke	Receiving inpatient stroke rehabilitation (United States)	270	1.1%			Kumar, 1998 [32]

[a] From pharmaceutical industry databases of clinical trial data used for post-marketing analyses. Reports of HU were presumed to be adverse events but the article did not specify

[b] The purpose of this study was to evaluate the Dexamethasone Symptom Questionnaire (DSQ)

[c] GER: gastro-esophageal reflux

[d] This was a telephone survey study

[e] Retrospective analysis of 11 symptomatic hyponatremia patients from a Veterans Administration Medical Center in Texas

[f] Patient data from 14 medical centers

[g] Initial treatment in previously chemotherapy-naïve patients

[h] Newly diagnosed patients

[i] Single medical center study

[j] NMO: neuromyelitis optica

[k] NMOSD: neuromyelitis optica spectrum disorder

[l] LMA: laryngeal mask airway

[m] Subpopulation of 12 patients was derived from Table 2 data in the source article

[n] D & C: dilation and curettage

literature reviewed, clinical consequences of HU could be devastating, far-reaching, and detrimental to both physical and mental health. While severity was commonly indicated by HU episode duration, we also found that clinical consequences in a given patient were a function of the medical context of that patient. While our review is limited by a large proportion of case studies, we also note that the variety and potential severity of HU consequences can be well appreciated at the level of detail with which case reports are presented.

Nutrition and Sleep Impairments

Several studies found that chronic HU impaired post-operative recovery by interfering with nutritional intake and sleep [11, 12, 14, 17, 19–22, 24, 34, 54, 55]. A retrospective chart review of patients ($N = 28$) with treatment-resistant persistent HU by Kim et al. found it caused weight loss (14.29%), insomnia (28.57%), and dyspnea (21.43%) [56••]. Marsot-Dupuch et al. reported a study of idiopathic intractable HU ($N = 9$) that found two patients experienced "extreme weight loss" (> 12 kg) [59]. Other articles reported that patients lost between 16 and 42 pounds due to persistent HU [18, 19, 58].

In a case report, Patel et al. described a 69-year-old man with intermittent HU (weekly for 3 months) that began when he started using a continuous positive airway pressure (CPAP) machine for sleep apnea [59]. After several HU treatments failed, he stopped using the CPAP in order to resolve his HU, preferring to leave his apnea untreated than to endure intermittent HU [59].

Complications in Cancer and Palliative Care

The one published HU guideline noted that HU puts patients at high risk for aspiration pneumonia, dehydration, electrolyte imbalance, cardiac arrhythmias, wound dehiscence, and depression [15, 60–63]. Case reports also describe HU as causing dyspnea, vomiting, anorexia, insomnia, anxiety, and depression [15, 62].

A case-controlled study of cancer patients with HU ($N = 16$) by Ge et al. found that HU resolution resulted in ($p < 0.0001$) reductions of patient discomfort, distress, and fatigue as well as difficulty swallowing ($n = 4$), sleeping ($n = 2$), breathing ($n = 2$), and speaking ($n = 1$) and diaphragmatic pain ($n = 1$), cough ($n = 1$), and nausea/vomiting ($n = 1$) [13].

HU have also been reported to interfere with cancer diagnostics and treatment. In one case report, Son et al. reported that intermittent HU episodes (over 4 days) had to be resolved before the patient could undergo an MRI [64]. Errante et al. report a patient with metastatic colon cancer whose persistent HU prevented completion of chemotherapy [65].

Gastro-esophageal Complications

Patients with HU often develop gastro-esophageal symptoms such as chest discomfort, retrosternal pain, nausea, vomiting, and GER [18, 19, 21, 22, 62, 66–68]. Multiple articles specifically associated HU with development of GER which was hypothesized to occur due to increased gastric pressure and/or negative intra-esophageal pressure during the diaphragmatic spasm [9]. It was noted that GER could then lead to additional complications including strictures, esophagitis, and esophageal ulcer [9]. In a large survey of GER patients ($N = 2500$), Rey et al. found that 9% considered their HU to be problematic [40]. Reflux was also associated with HU in anesthetized patients, with an estimated 40% of those who developed HU under sedation also developing GER [47, 67].

Complications with Sedation

Several articles addressed HU in sedated patients [47, 50, 69–73]. Kranke et al. reported that HU can impede endoscopy by disrupting spontaneous respiration [73]. There were also reports of reflux, regurgitation, and aspiration in anesthetized patients who developed HU during endoscopic procedures [67, 74]. One case report by Landers et al. described a pediatric patient who repeatedly developed HU with propofol and, on one occasion, experienced laryngospasm that required additional sedation and bag-valve-mask ventilation [72]. In a randomized, double-blind study of patients undergoing dilatation and curettage ($N = 200$), Weksler et al. concluded that lidocaine pre-treatment should be used to prevent methohexitone-induced HU in sedated, non-intubated patients to reduce risk of airway obstruction, decreased minute ventilation and respiratory frequency, and apnea [50].

A case study by Zhang et al. reported a patient who developed persistent HU during surgery; ultimately, the surgical team resorted to a right phrenic nerve block in order to continue the operation [70]. The authors warned that risk for dyspnea should be carefully considered when conducting phrenic nerve block during surgery [70].

Cardiovascular complications including bradycardia and pathological hemodynamic changes such as systolic hypotension have been reported in sedated patients with co-morbid heart disease and HU [47, 75, 76]. These events were associated with acute negative intrathoracic pressure precipitated by HU, but it is unknown whether systolic hypotension due to HU is detrimental [47]. In a case report, Samuels described HU-associated hematemesis "due to rupture of the cardio-esophageal veins, following edema and engorgement" from continuous diaphragmatic spasms [58].

Hiccups may be particularly problematic in ventilated infants [71, 77]. A case study of an encephalopathic infant by Panayiotou et al. noted that HU was misinterpreted as

spontaneous breathing by the ventilator (tidal-volume targeted ventilation) instead of abnormal diaphragmatic contractions [79]. These misinterpretations complicated accurate assessment and treatment.

Complications in Stroke

Intractable HU were reported to have substantial clinical consequences for stroke patients, including exhaustion that prevented rehabilitation [12, 32, 78]. Intractable HU have been associated with poor oral intake leading to malnutrition, weight loss, and dehydration [12]. Post-stroke dysphagia puts many of these patients at risk for regurgitation, aspiration, and aspiration pneumonia during an HU episode [12]. In a case-controlled study of 90 patients with LMI ($n = 24$ with HU vs. $n = 66$ without HU), Moon et al. found that those with HU had significantly higher rates of aspiration pneumonia ($p = 0.0001$; 50% vs. 13.6%, respectively) [79]. A case series in stroke patients with intractable HU ($N = 3$) reported by Kumar et al. found poor rehabilitation outcomes, including one patient who lost 35 pounds despite tube feeding and nutrition consultation [32].

Mental Health Complications

A case series ($N = 11$) reported by Cronin found that seven patients developed psychogenic polydipsia with hyponatremia as a result of excessive water consumption aimed at curing their HU [31]. These patients required multiple hospital admissions for confusion, lethargy, a semi-comatose or comatose state, and seizures [31].

In a case report, Sanchak described a patient who was hospitalized for HU with nausea, reflux, belching, and vomiting accompanying each hiccup and who became sleep deprived and disoriented [68]. During hospitalization, he fell while walking which was described as "secondary to HU" and attributed to combined effects of sleep deprivation and medications used to treat his HU [68].

Several case reports described persistent HU as precipitating onset of psychiatric conditions including depression and anxiety. In a review article, Cunningham described stroke patients with persistent HU as having higher risk for developing depressive illness [12]. A case study of a patient with Addison's disease reported by Hardo described clinical depression due to persistent HU [80]. Walker et al. reported

Table 2 Quality of life impacts of hiccups

Source	ADL[a] impacts	Psychological impacts
Palese, 2014 [23] Case series Cancer patients ($N = 5$)	Patients report: muscle pain, trouble breathing, unable to communicate, eat, or sleep, restrict activity to avoid triggering HU, muffle HU sounds to avoid upsetting family members, "very tiring", "debilitating"	Patients report: "constant tension", "despair", "anguish", "powerless", "overwrought"
Ge, 2010 [13] Case controlled study Cancer patients ($N = 16$)	Authors note: "Hiccups have a significant impact on patient activities of daily living."	
Jatzko, 2007 [89] Case series Cardiac patients ($N = 3$)		Patients report: "very distressing" "unbearable"
Arnulf, 1996 [34] Case series HU patients ($N = 8$)	Authors report: significant sleep disturbances, latency periods twice as long as in patients without HU, deficient slow wave sleep, deficient, REM sleep, overall poorer sleep quality in those with HU	
Mercadante, 2013 [43] Prospective cohort study Cancer patients ($N = 48$; $n = 14$ with HU[a])	Authors state: "The burden of these symptoms has never been assessed."	Authors state: "While prevalence may be low, the distress these symptoms cause patients and their families may be high."
Mirijello, 2013 [21] Case series IM patients ($N = 7$)	Authors state: reduced QoL, patients are unable to eat or sleep	Authors state: "a worrying symptom for patients", "HU induces in patients the fear of being affected by a serious disease"
Kumar, 1998 [32] Case series Stroke patients ($N = 3$)		Authors state: patients became "overwrought" and "frustrated"
Ferdinand, 2012 [12] Review article Stroke patients with HU	Authors state: reduced QoL, patients are unable to eat, sleep, or carry on conversation	Authors state: "frustrates patients with dysarthria, dysphonia, or expressive dysphasia"

[a] ADLs: activities of daily living which include but are not limited to eating, speaking, sleeping, attending social events, going to school, and working

HU hiccups, *REM* rapid eye movement, *IM* internal medicine, *QoL* quality of life

two other cases, describing bouts of intermittent HU in advanced cancer patients as provoking "extreme anxiety" and "panic attacks" [82]. A case reported by Lee et al. described a college professor with idiopathic, intractable HU who received psychological treatment for 5 years due to his HU [18]. Another case reported by Maximov et al. was of a post-myocardial infarction patient whose HU (8 months duration) caused anxiety requiring medical treatment [19].

Quality of Life Consequences

HU can have devastating impacts on QoL. One study ($N = 45$) reported by Go et al. randomized corticosteroid rotation to assess QoL in a subgroup ($n = 29$) using the Functional Assessment of Cancer Therapy-General version 4 (FACT-G, v4) [38]. There was no major, overall QoL differences between treatment arms (mean total scale scores: 71.5 for dexamethasone vs. 71.7 for methylprednisolone) [38]. Scores for the HU sub-group were not reported which is unfortunate, as normative population scores for the FACT-G are available and may provide insight to the burden of HU in terms of QoL.

Palese et al. conducted a phenomenological study of five neuro-oncology patients with persistent HU (> 48 h) and reported that HU have a devastating impact on QoL for patients and their families [23]. The impact of HU on QoL was characterized by three main themes of patients: (1) resignation to its unpredictable nature (with the unpredictability of HU inducing both hyper-vigilance for the next episode and resignation that it would occur); (2) desperation (as each HU episode was very tiring and consumed a lot of energy with some episodes causing muscle pain that was "much more dramatic than the pain of other symptoms suffered during the cancer illness trajectory"); (3) learning to control the pauses between HU (as those who did not find effective treatment learned how to increase the pauses between HU in order to cope) [23].

Multiple case reports provided further insight into consequences of HU on QoL, describing it as exhausting, distressing, restricting, disruptive, uncomfortable, irritating, constant, intense, detrimental, frustrating, disabling, depressing, causing tearfulness, interfering, fatiguing, embarrassing, work preventing, isolating, stressful, anxiety-provoking, nauseating, debilitating, annoying, incessant, painful, and unpredictable [2–5, 7•, 10–12, 14, 17–20, 22, 24, 62, 60, 65, 66, 80–87]. Notably, two cases of advanced cancer patients reported by Wilcock et al. and Zylicz indicated that HU were so distressing, patients requested to die or threatened suicide to end the episode [62, 68]. Table 2 summarizes QoL findings from studies excluding single case reports.

The impact of HU on ADLs was the basis of scoring in the Hiccups Assessment Instrument (HAI) developed by Ge et al. with scores of 1–3 reflecting "nagging but interfering little with ADLs"; 4–6 reflecting "significant interference with ADLs"; and 7–10 reflecting "disabling and unable to perform ADLs" [13]. In their study of 16 cancer patients undergoing acupuncture, Ge et al. found a mean HAI severity score of 5.2 which they described as "warranting medical attention" [13].

Consumption of Healthcare Resources and Cost Consequences

No studies directly investigated direct/indirect medical costs of HU, but several indicated that HU is associated with increased use of healthcare resources and, thus, costs.

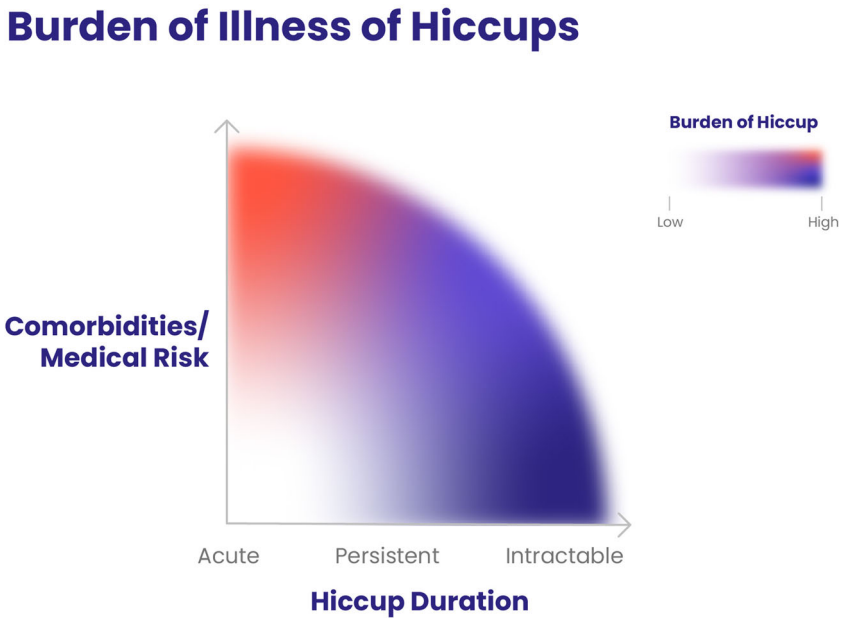

Fig. 1 Proposed interaction of HU duration and patient comorbidities/medical risk* to increase burden**. Illustration is conceptual and not based on data. Future studies are needed to quantify numeric values and rate of increasing burden. *Medical risk is defined as patient status based on current health conditions and treatments being received including surgery, sedation, and ventilation. **Burden is defined as clinical, QoL, and economic consequences. Acute HU: ≤ 48 h; persistent HU: 48 h to 1 month; intractable HU: > 1 month

Use of Outpatient and Inpatient Services

Multiple case reports described hospital admissions for HU after patients tried but failed to resolve them at home [3, 9, 11, 12, 17, 18, 21, 22, 31, 62, 82, 90]. Prior to hospital admission, most patients sought outpatient treatment from primary care physicians or emergency departments which was often ineffective or only temporarily effective [3, 11, 17, 18, 21, 31].

Hospitalization was most often reported among patients with pre-existing conditions who developed HU. One case reported within a review article by Ferdinand described a stroke patient with multiple hospital admissions for dehydration secondary to persistent HU who was eventually referred for surgical HU treatment [12]. One patient in a case series ($N = 11$; $n = 7$ with HU) reported by Cronin received Social Security disability payments for 15 years due to intractable HU and was hospitalized 24 times for HU-associated hyponatremia [31]. Two other patients in this case series were hospitalized for HU 16 times and 7 times, respectively [31].

In addition, patients with HU were reported to develop psychiatric conditions requiring mental health care including anxiety and depression [12, 19, 22, 80, 81].

Length of Hospital Stay

In a retrospective study of stroke patients, Kumar et al. found that those who developed HU had an average of nine additional hospital days compared to those without HU [32]. Additional days were attributed to fatigue and exhaustion (due to HU spasms and side effects of pharmacological HU treatments) that prevented participation in rehabilitation [32]. A review article by Ferdinand summarizing the impact of HU on stroke rehabilitation also noted that it could hinder rehabilitation [12]. A case-controlled study in stroke patients ($N = 90$) by Moon et al. found significantly longer average hospital stays ($p = 0.03$) in those with HU (38.0 [± 42.1] days) than in those without HU (21.1 [± 31.6] days) [79]. This difference was partly attributed to significantly higher rates of aspiration pneumonia ($p = 0.0001$) in HU patients [79].

Diagnostic Testing

Because HU can be a symptom of other serious conditions, the search for a cause frequently involves multiple diagnostic investigations including neurological workups, blood biochemistry tests, thyroid function tests, CNS imaging, computed tomography scans, urinalysis, antibody and anti-DNA tests, gastroenterology evaluations, psychiatric consultations, ultrasonography, chest x-rays, and electrocardiograms [5, 9, 10, 17, 19, 21, 24, 54, 57, 66, 78, 84, 91–94]. Notably, testing did not always identify the cause, and identifying the cause did not always lead to effective treatment.

Ineffective Palliation

The lack of treatment guidelines and treatments that are effective across all patient populations necessitated a "trial and error" approach which appears to lead to inefficient care and higher costs [2–4, 43, 53, 95, 96]. Approximately 50 medical treatments for HU (excluding folk remedies such as breath holding and water drinking) were reported, ranging from gastro-intestinal and psychoactive medications to invasive procedures such as upper cervical epidural block, phrenic nerve block or dissection, paravertebral nerve block (T7-T12), stellate ganglion block, and Nissen fundoplication [2, 5, 7•, 9–14, 16, 17, 19–21, 24, 32, 33, 54, 58, 62, 70, 78, 80, 82–85, 87, 89–94, 99–103]. Alternative therapies including acupuncture and osteopathic manipulation were also used to treat HU [13, 97].

Pharmacologic HU treatments that were sequentially administered and withdrawn upon failure produced side effects including sedation, dizziness, insomnia, weakness, ataxia, tachycardia, postural hypotension, and confusion that may cause increased healthcare costs [2, 3, 7•, 14, 16, 19–22, 24, 32, 50, 64, 78, 81, 89–91, 94]. Opiates such as hydromorphone were also sometimes prescribed to manage pain caused by constant diaphragmatic spasm and to sedate agitated or exhausted patients [15, 20, 22, 60, 64, 70]. The addictive risks and side effects of opiates are well documented elsewhere. Notably, despite having so many therapeutic options, HU often remained unresolved or only resolved temporarily.

Conclusion

This review characterizes the burden of HU and shows, overall, that it is sizable, wide-ranging, and includes high morbidity, negative QoL impacts, and increased healthcare resource utilization with a presumed increase in healthcare costs. The fact that the ramifications of HU include extreme suffering is duly noted. In general, the severity of these consequences varies with both the patient's pre-existing health status and the duration of HU. However, even relatively short HU episodes may have serious consequences in patients with underlying health issues. Thus, HU may be best understood as a physiologic event that can complicate existing medical conditions and treatments regardless of duration of the HU episode (Fig. 1).

A few additional, salient points arise from this systematic review. First, the often mundane aspect of HU—or the mere fact that anyone and everyone has had HU from time-to-time—belies the potential gravity of HU. Second, the fact that current HU therapy relies on trial and error only seems to detract from patient QoL in refractory HU and escalate the morbidity and costs of HU. Finally, the burden of HU has not been well studied. Seventy percent of the literature that describes the HU burden is from case studies.

For now, available studies provide some understanding of what patients with HU experience. There were strong anecdotal observations that HU can have a devastating impact on QoL, but data using validated QoL instruments are needed to quantify that burden. A better understanding of HU burden is needed to facilitate clinical decision-making and avoid potential clinical and economic consequences. Further research is needed to clarify relationships between patient health status and HU duration, characterize populations at risk for HU, and identify situations in which problematic HU can be anticipated and prevented.

Compliance with Ethical Standards

Conflict of Interest Katharine Hendrix has received compensation from Meter Health, Inc. for assistance with literature review, research, analysis, and preparation of this manuscript.

David Wilson receives compensation from and holds equity in Meter Health, Inc.

MJ Kievman is a founder of and holds equity in Meter Health, Inc. She is also an inventor on issued U.S. patent 8,563,030 (assigned to Meter Health, Inc.) and is also a co-inventor on pending U.S. patent 62/835,691 (assigned to Meter Health, Inc.)

Aminah Jatoi declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lupton T. A thousand notable things of Sundrie Sortes: Wherof some are Wonderfull, some Straunge, some pleasant, Diuers necessary, a great Sort profitable and many very precious. Second ed. London: E. Allde for N. Fosbrooke; 1627.
2. Arsanious D, Khoury S, Martinez E, Nawras A, Filatoff G, Ajabnoor H, et al. Ultrasound-guided phrenic nerve block for intractable hiccups following placement of esophageal stent for esophageal squamous cell carcinoma. Pain Physician. 2016;19: e653–e6.
3. Alshammary S, Duraisamy B, Saleem LA, Al Fraihat L, Altamimi A, Brown S. Palliative management of intractable hiccups in a patient with an advanced brain tumour. J Health Spec. 2016;4(4):294. https://doi.org/10.4103/2468-6360.191913.
4. McGrane IR, Shuman MD, McDonald RW. Donepezil-related intractable hiccups: a case report. Pharmacotherapy. 2015;35(3): e1–5. https://doi.org/10.1002/phar.1551.
5. Ozturk O, Yavuz E, Yazicioglu B, Uzuner B. Treatment of resistant idiopathic hiccups with pulse radio frequency on phrenic nerve and gabapentin: a case report. Niger J Clin Pract. 2017;20(7):910–3. https://doi.org/10.4103/1119-3077.212438.
6. Chang FY, Lu CL. Hiccup: mystery, nature and treatment. J Neurogastroenterol Motil. 2012;18(2):123–30. https://doi.org/10.5056/jnm.2012.18.2.123.
7. • 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 Esp. 2017;68(2):98–105. https://doi.org/10.1016/j.otoeng.2017.02.005 **This retrospective study of 37 patients with persistent hiccups identified potential etiologies in 24 (65%) cases. Three patients required hospitalization to reduce hiccups severity, and 5 of 22 cases with follow-up data recurred after succesful treatment, requiring additional therapy. The multidisciplinary challenges of hiccups management are discussed.**
8. Giugni J, Seijo D, Micheli F. Are hiccups non-motor symptoms? Parkinsonism Relat Disord. 2010;16(10):690. https://doi.org/10.1016/j.parkreldis.2010.07.013.
9. Chongsrisawat V. al e. Intractable hiccups and gastroesophageal reflux disease attributable to brain tumor: A case report. Biomed J Sci Tech Res. 2018;2(2). doi: https://doi.org/10.26717/BJSTR.2018.02.000732.
10. Liang C, et al. Gabapentin therapy for persistent hiccups and central post-stroke pain in a lateral medullary infarction — two case reports and literature review. Tzu Chi Med J. 2005;17:365–8.
11. Cunningham VL. Benztropine for the treatment of intractable hiccups: new indication for an old drug? Cjem. 2015;4(03):205–6. https://doi.org/10.1017/s1481803500006394.
12. Ferdinand P. Intractable hiccups post stroke: Case report and review of the literature. J Neurol Neurophysiol. 2012;03(05). https://doi.org/10.4172/2155-9562.1000140.
13. Ge AX, Ryan ME, Giaccone G, Hughes MS, Pavletic SZ. Acupuncture treatment for persistent hiccups in patients with cancer. J Altern Complement Med. 2010;16(7):811–6. https://doi.org/10.1089/acm.2009.0456.
14. Kako J, Kobayashi M, Kanno Y, Tagami K. Intranasal vinegar as an effective treatment for persistent hiccups in a patient with advanced cancer undergoing palliative care. J Pain Symptom Manag. 2017;54(2):e2–4. https://doi.org/10.1016/j.jpainsymman.2017.02.011.
15. Krakauer E, Zhu AX, Bounds BC, Sahani D, McDonald K, Brachtel EF. A 58-year-old man with esophageal cancer and nausea, vomiting, and intractable hiccups. N Engl J Med. 2005;352: 817–25.
16. Kuusniemi K, Pyylampi V. Phrenic nerve block with ultrasound-guidance for treatment of hiccups: a case report. J Med Case Rep. 2011;5:493. https://doi.org/10.1186/1752-1947-5-493.
17. Laoutid J, al e. successful treatment of persistent idiopathic hiccup with ondansetron. Int J Med Health Res. 2017;3(3):39–41.
18. Lee JH, Kim TY, Lee HW, Choi YS, Moon SY, Cheong YK. Treatment of intractable hiccups with an oral agent monotherapy of baclofen -a case report. Korean J Pain. 2010;23(1):42–5. https://doi.org/10.3344/kjp.2010.23.1.42.
19. Maximov G, Kamnasaran D. The adjuvant use of lansoprazole, clonazepam and dimenhydrinate for treating intractable hiccups in a patient with gastritis and reflux esophagitis complicated with myocardial infarction: a case report. BMC Res Notes. 2013;6: 327–30.
20. Menon M. Gabapentin in the treatment of persistent hiccups in advanced malignancy. Indian J Palliat Care. 2012;18:138–40.
21. Mirijello A, Addolorato G, D'Angelo C, Ferrulli A, Vassallo G, Antonelli M, et al. Baclofen in the treatment of persistent hiccup: a case series. Int J Clin Pract. 2013;67(9):918–21. https://doi.org/10.1111/ijcp.12184.
22. Moro C, Sironi P, Berardi E, Beretta G, Labianca R. Midazolam for long-term treatment of intractable hiccup. J Pain Symptom

Manag. 2005;29(3):221–3. https://doi.org/10.1016/j.jpainsymman.2005.01.001.
23. Palese A, Condolo G, Dobrina R, Skrap M. Persistent hiccups in advanced neuro-oncology patients. J Hosp Palliat Nurs. 2014;16(7):396–401. https://doi.org/10.1097/njh.0000000000000087.
24. Wilcox SK, Garry A, Johnson MJ. Novel use of amantadine: to treat hiccups. J Pain Symptom Manag. 2009;38(3):460–5. https://doi.org/10.1016/j.jpainsymman.2008.10.008.
25. Fleet W, Morgan H, Morello P. A fatal case of hiccups. J Tenn Med Assoc. 1990;83(2):79–80.
26. Twycross R, Reginard C. Dysphagia, dyspepsia, and hiccup. In: Doyle D, Hanks G, MacDonald N, editors. Oxford textbook of palliative medicine. Second ed. Oxford: Oxford University Press; 1993. p. 291–9.
27. Guelaud C, Similowski T, Bizec J, Cabane L, Whitelaw W, Derenne J. Baclofen therapy for chronic hiccup. Eur Respir J. 1995;8(2):235–7.
28. Moretto E, Wee B, Wiffen P, Murchison A. Interventions for treating persistent and intractable hiccups in adults. Cochrane Database of Systematic Reviews. Hoboken: Wiley; 2013. p. 1–19.
29. Polito N, Fellows S. Pharmacologica interventions for intractable and persistent hiccups: a systematic review. J Emerg Med. 2017;53(4):540–9.
30. Steger M, Schneemann M, Fox M. Systemic review: the pathogenesis and pharmacological treatment of hiccups. Aliment Pharmacol Ther. 2015;42(9):1037–50. https://doi.org/10.1111/apt.13374.
31. Cronin R. Psychogenic polydipsia with hyponatremia: report of eleven cases. Am J Kidney Dis. 1987;9(5):410–6. https://doi.org/10.1016/s0272-6386(87)80144-0.
32. Kumar A, Dromerick A. Intractable hiccups during stroke rehabilitation. Arch Phys Med Rehabil. 1998;79:697–9.
33. Takahashi T, Miyazawa I, Misu T, Takano R, Nakashima I, Fujihara K, et al. Intractable hiccup and nausea in neuromyelitis optica with anti-aquaporin-4 antibody: a herald of acute exacerbations. J Neurol Neurosurg Psychiatry. 2008;79(9):1075–8. https://doi.org/10.1136/jnnp.2008.145391.
34. Arnulf I, Boisteanu D, Whitelaw W, Cabane J, Garma L, Derenne J. Parasomnias chronic hiccups and sleep. Sleep. 1996;19(3):227–31.
35. Kohse E, Hollmann M, Bardenheuer H, Kessler J. Chronic hiccups: an underestimated problem. Anesth Analg. 2017;125(4):1169–83.
36. Lewis J. Hiccups: causes and cures. J Clin Gastoenterol. 1985;7:539–52.
37. Takiguchi Y, et al. Hiccups as an adverse reaction to cancer chemotherapy. J Natl Cancer Inst. 2002;94(10):772–4.
38. Go S, Koo D, Kim S, Song H, Kim R, Jang J, et al. Antiemetic corticosteroid rotation from dexamethasone to methylprednisolone to prevent dexamethasone-induced hiccup in cancer patients treated with chemotherapy: a randomized, single-blind, crossover phase III trial. Oncologist. 2017;22:1354–61.
39. Dore MP, Pedroni A, Pes GM, Maragkoudakis E, Tadeu V, Pirina P, et al. Effect of antisecretory therapy on atypical symptoms in gastroesophageal reflux disease. Dig Dis Sci. 2007;52(2):463–8. https://doi.org/10.1007/s10620-006-9573-7.
40. Rey E, Elola-Olasoa C, Rodrıguez-Artalejob F, Locke G, Dıaz-Rubio M. Prevalence of atypical symptoms and their association with typical symptoms of gastroesophageal reflux in Spain. Eur J Gastroenterol Hepatol. 2006;18(9):969–75.
41. Liaw C, Wang CH, Chang HK, Wang HM, Huang JS, Lin YC, et al. Cisplatin-related hiccups: male predominance, induction by dexamethasone, and protection against nausea and vomiting. J Pain Symptom Manage. 2005;30(4):359–66.
42. Parlak M, Sancak T, Arat M, Bilgiç S, Sanlıdilek U. Tunneled catheters placed in bone marrow transplant patients: radiological and clinical follow-up results. Diagn Interv Radiol. 2006;12:190–4.
43. Mercadante S, Porzio G, Valle A, Fusco F, Aielli F, Adile C, et al. Orphan symptoms in advanced cancer patients followed at home. Support Care Cancer. 2013;21(12):3525–8. https://doi.org/10.1007/s00520-013-2007-0.
44. Vardy J, Chiew K, Galica J, Pond G, Tannock I. Side effects associated with the use of dexamethasone for prophylaxis of delayed emesis after moderately emetogenic chemotherapy. Br J Cancer. 2006;94:1101–015.
45. Yang C, Wu C, Liaw C. Combination of palonosetron, aprepitant, and dexamethasone as primary antiemetic prophylaxis for cisplatin-based chemotherapy. Biom J. 2016;39:60–6.
46.•• Hosoya R, Tanaka I, Ishii-Nozawa R, Amino T, Kamata T, Hino S, et al. Risk factors for cancer chemotherapy-induced hiccups (CIH). Pharmacol Pharm. 2018;9:331–43 **This study assessed the risk factors for hiccups associated with chemotherapy in 292 patients. Male gender, nausea and vomiting, dexamethasone, cisplatin, and epoposide were identified as independent risk factors.**
47. Liu CC, Lu CY, Changchien CF, Liu PH, Perng DS. Sedation-associated hiccups in adults undergoing gastrointestinal endoscopy and colonoscopy. World J Gastroenterol. 2012;18(27):3595–601. https://doi.org/10.3748/wjg.v18.i27.3595.
48. Kremer L, Mealy M, Jacob A, Nakashima I, Cabre P, Bigi S, et al. Brainstem manifestations in neuromyelitis optica: a multicenter study of 258 patients. Mult Scler. 2014;20(7):843–7. https://doi.org/10.1177/1352458513507822.
49. Bapat P, Joshi R, Young E, Jago R. Comparison of propofol versus thiopentone with midazolam or lidocaine to facilitate laryngeal mask insertion. Can J Anaesth. 1996;43(6):564–8.
50. Weksler N, Stav A, Ovadiam L, Berman M, Segal A, Ribac L, et al. Lidocaine pretreatment effectively decreases the incidence of hiccups during methohexitone administration for dilatation and curettage. Acta Anaesthesiol Scand. 1992;36:772–4.
51. Chang J-M, Hwang S-J, Kuo H-T, Tsai J-C, Guh J-Y, Chen H-C, et al. Fatal outcome after ingestion of star fruit (Averrhoa carambola) in uremic patients. Am J Kidney Dis. 2000;35(2):189–93. https://doi.org/10.1016/s0272-6386(00)70325-8.
52. 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. J Pain Symptom Manag. 2016;51(2):278–83. https://doi.org/10.1016/j.jpainsymman.2015.09.013.
53. Doan J, Truong L, Reher P, Doan N. A case report of persistent hiccups following oral dexamethasone used in a dental implant regenerative procedure. Acta Sci Dent Sci. 2018;2(9):99–102.
54. Musumeci A, Cristofori L, Bricolo A. Persistent hiccup as presenting symptom in medulla oblongata cavernoma: a case report and review of the literature. Clin Neurol Neurosurg. 2000;102:13–7.
55. Neeno TA, Rosenow EC. Intractable hiccups-to the editor. Chest. 1996;110(4):1129–30. https://doi.org/10.1378/chest.110.4.1129.
56.•• Kim JE, Lee MK, Lee DK, Choi SS, Park JS. Continuous cervical epidural block: treatment for intractable hiccups. Medicine (Baltimore). 2018;97(6):e9444. https://doi.org/10.1097/MD.0000000000009444 **This prospective cohort study of continuous cervical epidural block (CCEB) in 28 patients with intractable hiccups and history of unsuccessful medical and invasive treatment, found CCEB was effective, requiring from 1–3 administrations to achieve complete remission.**
57. Marsot-Dupuch K, Bousson V, Cabane J, Tubiana J. Intractable hiccups: the role of cerebral MR in cases without systemic cause. Am J Neuroradiol. 1995;16:2093–100.

58. Samuels L. Hiccup: a ten year review of anatomy, etiology, and treatment. Can Med Assoc J. 1952;67:315–22.
59. Patel N, O'Brien K. Persistent singultus: Addressing complexity with simplicity. ACG Case Rep J. 2015;2(3):150–1. https://doi.org/10.14309/crj.2015.37.
60. British Columbia Center for Palliative Care. Hiccoughs. BC Inter-Professional Palliative Symptom Management Guidelines. New Westminster: BC Center for Palliative Care; 2017.
61. Marinella M. Diagnosis and management of hiccoughs in the patient with advanced cancer. J Support Oncol. 2009;7(4):122–7.
62. Wilcock A, Twycross R. Midazolam for intractable hiccup. J Pain Symptom Manag. 1996;12:59–61.
63. Phillips R. The management of hiccoughs in terminally ill patients. Nurs Times. 2005;101(31):32–3.
64. H-w S, Cho YW, Y-u K, Y-j S. Stellate ganglion block for the treatment of intractable hiccups - A case report. Anesth Pain Med. 2018;13(2):192–6. https://doi.org/10.17085/apm.2018.13.2.192.
65. Errante D, Bernardi D, Bianco A. Recurrence of exhausting hiccup in a patient treated with chemotherapy for metastatic colon cancer. Gut. 2005;54:1500–8.
66. Shay S, Myers R, Johnson L. Hiccups associated with reflux esophagitis. Gastroenterology. 1984;87:204–7.
67. Vanner R. Gastro-oesophageal reflux and hiccup during anaesthesia. Anaesthesia. 1993;48:92–3.
68. Sanchak K. Hiccups: when the diaphragm attacks. J Palliat Med. 2004;7(6):870–3.
69. McVey F, Goodman N. Gastro-oesophageal reflux and hiccough on induction of anaesthesia. Anaesthesia. 1992;47:712.
70. Zhang Y, Duan F, Ma W. Ultrasound-guided phrenic nerve block for intraoperative persistent hiccups: a case report. BMC Anesthesiol. 2018;18(1):123–4. https://doi.org/10.1186/s12871-018-0589-2.
71. Brouillette R, Thach B, Abu-u-Osba Y, Wilson S. Hiccups in infants: characteristics and effects on ventilation. J Pediatr. 1980;96:219–25.
72. Landers C, Turner D, Makin C, Zaglul H, Brown R. Propofol associated hiccups and treatment with lidocaine. Anesth Analg. 2008;107(5):1757–8.
73. Kranke P, Eberhart L, Morin A, Cracknell J, Greim C, Roewer N. Treatment of hiccup during general anaesthesia or sedation: a qualitative systematic review. Eur J Anaesthesiol. 2003;20:239–44.
74. Wang C, Sun S, Hsieh T, Yen K, Wu Y, Lin Y, et al. Unexpected left-sided pulmonary aspiration misdiagnosed as malignancy in PET cancer screening follllowing panendoscopy cancer screening under conscious sedation. Clin Nucl Med. 2010;35:604–6.
75. Rousseau P. Hiccups. South Med J. 1995;88:175–81.
76. Mathew O. Effects of transient intrathoracic pressure changes (hiccups) on systemic arterial pressure. J Appl Physiol. 1997;83:371–5.
77. Panayiotou E, Spike K, Morley C, Belteki G. Ventilator respiratory graphic diagnosis of hiccupping in non-ketotic hyperglycinaemia. BMJ Case Rep. 2017;2017. https://doi.org/10.1136/bcr-2017-220267.
78. Meng K, Yiang C, Nijanth M, Ashfaq L. Use of baclofen in the treatment of persistent hiccups: report of two cases. Arc Cas Rep C Med. 2015;1(1):101–4.
79. Moon C, Hwang S, Hong S, Jung S, Kwon S. Lesional location of intractable hiccups in acute pure lateral medullary infarction. Neurol Asia. 2014;19(4):343–9.
80. Hardo P. Intractable hiccups - an early feature of Addison's disease. Postgrad Med J. 1989;65:918–9.
81. Walker P, Watanabe S, Bruera E. Baclofen: a treatment for chronic hiccup. J Pain Symptom Manag. 1998;16:125–32.
82. Cersosimo R, Brophy M. Hiccups with high dose dexamethasone administration. Cancer. 1998;82(2):412–4.
83. Dunst M, Margolin K, Horak D. Lidocaine for severe hiccups. NEJM. 1993;329(12):890–1.
84. Walstra C, Reynaert H. Therapeutic gastroscopy in idiopathic persistent hiccups: A case report. J Gastrointest Dig Syst. 2016;06(02). https://doi.org/10.4172/2161-069x.1000400.
85. Wu Y, Wu Y, Chen L, Lin C. Hiccup secondary to amantadine in traumatic brain injury: A case report. Austin Neurol Neurosci. 2017;2(1):171–2
86. Ives T, Fleming M, Weart C, Bloch D. Treatment of intractable hiccups with intramuscular haloperidol. Am J Psychiatry. 1985;142:1368–9.
87. Peleg R, Peleg A. Case report: sexual intercourse as potential treatment for intractable hiccups. Can Fam Physician. 2000;46:1631–2.
88. Zylicz Z. Intractable hiccups caused by pulmonary embolism: a case report. Adv Palliat Med. 2010;9:149–52.
89. Jatzko A, Stegmeier-Petroianu A, Petroianu GA. Alpha-2-delta ligands for singultus (hiccup) treatment: three case reports. J Pain Symptom Manag. 2007;33(6):756–60. https://doi.org/10.1016/j.jpainsymman.2006.09.026.
90. Kutuk MO, Guler G, Tufan AE, Kutuk O. Hiccup due to aripiprazole plus methylphenidate treatment in an adolescent with attention deficit and hyperactivity disorder and conduct disorder: a case report. Clin Psychopharmacol Neurosci. 2017;15(4):410–2. https://doi.org/10.9758/cpn.2017.15.4.410.
91. de Hoyo A, Esparza E, Cervantes-Sodi M. Non-erosive reflux disease manifested exclusively by protracted hiccups. J Neurogastroenterol Motil. 2010;16(4):424–7.
92. Eisenacher A, Spiske J. Persistent hiccups (singultus) as the presenting symptom of medullary cavernoma. Dtsch Arztebl Int. 2011;108(48):822–6. https://doi.org/10.3238/arztebl.2011.0822.
93. Kockar C, İşler M, Cüre E, Şenol A, Baştürk A. Hiccup due to gastroesophageal reflux disease. Eur J Gen Med. 2009;6(4):262–4.
94. Matsuki Y, Mizogami M, Shigemi K. A case of intractable hiccups successfully treated with pregabalin. Pain Physician. 2014;17:e241–e2.
95. Seidel B, Benaquista-Desipio G. Use of osteopathic manipulative treatment to manage recurrent bouts of singultus. J Am Osteopath Assoc. 2014;114:660–4.
96. Thompson DF, Brooks KG. Gabapentin therapy of hiccups. Ann Pharmacother. 2013;47(6):897–903. https://doi.org/10.1345/aph.1S018.
97. Cheng CM, Tsai SJ. Persistent hiccups associated with switching from paliperidone to amisulpride. Psychiatry Clin Neurosci. 2015;69(6):383. https://doi.org/10.1111/pcn.12239.
98. Liaw C-C. Gender discrepancy observed between chemotherapy-induced emesis and hiccups. Support Care Cancer. 2001;9(6):435–41. https://doi.org/10.1007/s005200000231.
99. Marhofer P, Glaser C, Krenn C, Grabner C, Semsroth M. Incidence and therapy of midazolam induced hiccups in paediatric anaesthesia. Paediatr Anaesth. 1999;9:295–8.
100. Nishikawa T, Araki Y, Hayashi T. Intractable hiccups (singultus) abolished by risperidone, but not by haloperidol. Ann General Psychiatry. 2015;14:13. https://doi.org/10.1186/s12991-015-0051-5.
101. Kondo T, Tanigaki T, Suzuki H, Tamaya S, Ohta Y, Yamabayashi H. Long-standing hiccup in a patient with sarcoidosis. Jpn J Med. 1989;28(2):212–5.
102. Vaidya V. Sertraline in the treatment of hiccups. Psychosomatics. 2000;41(4):353–5.
103. Vantrappen G, Decramer M, Harlet R. High-frequency diaphragmatic flutter: symptoms and treatment by carbamazepine. Lancet. 1992;339:265–7.