

Managing hiccups

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You are called to see George, a 61-year-old man with proximal gastric cancer that has recently metastasized to his liver despite chemotherapy. He has had frequent short bouts of hiccups over the past few months, usually related to swallowing. For the past 6 hours his hiccups have persisted; because you are the doctor on call, you are contacted by the ward nurse. She wonders about getting an order for chlorpromazine for his hiccups.

Hiccups are diaphragmatic muscle contractions with early glottis closure terminating inspiration. They are involuntary and spasmodic, and often involve inspiratory intercostal muscle contractions. Hiccups are a common experience, and warrant treatment only when they become persistent and bothersome. If persistent, they can affect conversation, concentration, and oral intake, and can lead to frustration, fatigue, and insomnia. They might contribute to an increase in pain.

The prevalence of hiccups in terminal disease is not known. In general, they are more common in children, more common in adult men than in women, and more common in those with comorbid conditions. An individual's hiccup rate is usually consistent for each hiccup episode, occurring at a frequency of 4 to 60 hiccups per minute.¹

Hiccups are said to be *persistent* if they last more than 48 hours, and *intractable* if they last more than a month.² In the palliative care population, even a few days of hiccups might be extremely uncomfortable.

Causes of hiccups

The science of hiccups is still being elucidated. Current theories include an amorphous neural network coordinating various afferent inputs, functioning as a "hiccup centre," or some imbalance between inspiratory and expiratory neural circuitry, caused by stimulation or damage to the vagus nerve, the phrenic nerve, or the brainstem.^{3,4}

There are many potential causes of hiccups, most of which are gastrointestinal and involve vagal and phrenic nerve stimulation. Other causes include central nervous system disorders, metabolic disorders, psychogenic disorders, and drugs. Metabolic causes of hiccups include hypokalemia, hypocalcemia, hypocarbia (hyperventilation), and uremia. Interestingly, some of the same medications used to treat hiccups have also, at times, been implicated in their cause (eg, steroids, benzodiazepines, opioids, and antidopaminergics); this might be owing to the complexity of hiccup origin, possibly involving dopamine, serotonin, opioid, calcium channel, and γ -aminobutyric acid (GABA) pathways in the brainstem and medulla.^{3,4} A review of existing medications should precede the addition of more medication to manage hiccups.

Treating hiccups

A quick Internet search of *treating hiccups* yields more than 70 000 sites. Therein are listed all manner of "cures." Many of them involve some kind of glottic stimulation (eg, holding one's breath, drinking multiple gulps of water, drinking a glass of water upside down, eating a spoonful of peanut butter, chewing on a lemon, inhaling pepper to induce a sneeze). These simple treatments are sometimes effective, perhaps by stimulating or blocking some of the nerves involved in potentiating the hiccups. Some interventions involve increasing partial pressure of carbon dioxide (eg, breath holding

BOTTOM LINE

- Hiccups are a common human experience, but can create a great deal of physical and emotional discomfort in end-stage disease.
- Many treatments of hiccups are described, and some common nonmedical treatments might be effective.
- While the use of medications remains somewhat empirical, defoaming and propulsive agents, followed by baclofen if needed, are good initial choices.

POINTS SAILLANTS

- Le hoquet est une expérience commune chez l'humain, mais il peut causer beaucoup de malaise physique et émotionnel en phase terminale de la maladie.
- De nombreux traitements du hoquet sont décrits et certains traitements non médicaux courants pourraient être efficaces.
- Si l'utilisation des médicaments demeure plutôt empirique, les agents anti-mousse et pro-cinétiques, suivis par du baclofen, sont de bons choix initiaux.



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or breathing into a paper bag). Other potential cures seem more bizarre: digital rectal massage, for example (although it might be contraindicated in patients with neutropenia, where there is a concern that it might cause Gram-negative bacteremia).

A search for a pharmacologic treatment unfortunately also results in a wide selection of options. There are no large randomized controlled trials, nor any consensus statements, on how to treat hiccups. Medical treatment strategies, therefore, remain somewhat empirical. Most of our understanding of the use of medications for hiccups comes from case reports and small series of patients. As this is a brief review, only a few examples of case studies are specifically referenced.

Treatment of hiccups should be directed toward the specific cause, if one can be identified. Infections might be treatable. Brainstem lesions might respond to steroids or radiation. Biochemical abnormalities might be reversed. Frequently, persistent hiccups are idiopathic in nature. If they are persistent and bothersome, consider the addition of a medication to treat the hiccups, recognizing that adding medications might result in drug interactions and side effects.

Antipsychotic medications

Chlorpromazine: Chlorpromazine is the only medication approved for hiccups by the US Food and Drug Administration, and for many years it was the drug of choice.¹ Chlorpromazine is a dimethylamine derivative of phenothiazine. It acts centrally by dopamine antagonism in the hypothalamus. It has serious potential side effects, such as hypotension, urinary retention, glaucoma, and delirium, so it is generally no longer recommended as first-line

Suggested approach to managing hiccups

1. Use nonpharmacologic measures, particularly those which have been helpful in the past
2. Attempt simethicone, domperidone, or metoclopramide, or a proton pump inhibitor
3. Prescribe baclofen if renal function is reasonable
4. Add gabapentin
5. Attempt chlorpromazine or haloperidol if hiccups persist (or attempt at Step 3 if renal function is decreased)
6. Consider nifedipine, valproic acid, dexamethasone, or sertraline
7. Add midazolam

management. A usual dosage would be 25 mg 4 times a day, increasing to 50 mg 4 times a day if needed.

Haloperidol: Haloperidol has been shown to be effective, presumably also via dopamine antagonism. It might be better tolerated than chlorpromazine is.

Anticonvulsants. Valproic acid enhances GABA transmission centrally, and is similarly thought to aid in blocking the hiccup stimulus. Older anticonvulsants (valproic acid, phenytoin, carbamazepine) have been documented as potential treatments of hiccups for a number of decades, but challenges around their use include drug interactions and narrow therapeutic windows.

Gabapentin, a newer antiepileptic drug commonly used in cancer and palliative medicine for neuropathic pain management, produces a blockade of neural calcium channels and increases release of GABA, which might modulate diaphragmatic excitability. Gabapentin has no known serious drug interactions and is not hepatically metabolized. One study involving 43 patients noted improvement and reduction of hiccups in 32 patients with 900-mg doses daily and in 9 patients with 1200-mg doses daily.⁵ In all patients, gabapentin was given as an initial drug for the treatment of hiccups. There were no severe adverse effects observed. Twelve patients had transient sleepiness.

Defoaming agents. Defoaming agents such as simethicone might be helpful if gastric distention is present.

Prokinetic agents. Defoaming agents might work well with prokinetic agents such as domperidone and metoclopramide, which help empty the stomach of its contents. Metoclopramide also has central dopamine antagonism but less so than chlorpromazine.

Peppermint. Peppermint facilitates belching by relaxing the lower esophageal sphincter. Although this has been noted as a potential treatment of hiccups, there is little sense in using it along with a prokinetic agent, as their effects are somewhat opposite.⁴

Proton pump inhibitors. Proton pump inhibitors are important in the treatment of gastroesophageal reflux, which promotes hiccups. Proton pump inhibitors are generally safe and might be helpful in some cases.

Baclofen. Baclofen in dosages of 5 mg twice daily to 20 mg 3 times daily has been shown to be effective in alleviating hiccups in several small trials and case series since 1992.^{3,4,6,7} Although there are no well designed, large clinical trials, this GABA analogue leads to a perceptual blockage in synaptic transmission, and is now

considered the drug of choice for the treatment of hiccups. It does have limitations. It might not be well tolerated owing to potential ataxia, delirium, dizziness, and sedation. Baclofen-related delirium is more common in patients with renal failure; however, specific dose modifications for a reduced glomerular filtration rate have not been defined.

Nifedipine. Nifedipine, 10 to 20 mg orally or sublingually, might play a role in reversing the abnormal depolarization in the hiccup reflex arc, and case reports have shown it to be effective.⁸ But there is substantial risk of inducing hypotension, which might be especially severe in relatively volume-depleted patients, such as many of those receiving palliative care.

Methylphenidate. The neurostimulant methylphenidate might decrease hiccups through inhibition of dopamine and norepinephrine uptake.⁹ It might be a good choice in patients with concurrent depression or opioid-induced sedation, for which it might also be helpful.

Midazolam. Midazolam has been used effectively, administered as a continuous intravenous or subcutaneous infusion, short of producing sedation.⁴

Lidocaine. Intravenous infusion of lidocaine has terminated hiccups in postoperative patients, but there is considerable risk of cardiovascular and neurologic toxicities, particularly in patients with advanced disease.¹⁰ Nebulized lidocaine might be effective on sensory nerves, and it has a better side effect profile; however, risks of aspiration after nebulization should be considered.

Dexamethasone. Dexamethasone, although a main cause of hiccups, has been shown to terminate hiccups in AIDS-related progressive multifocal leukoencephalopathy, perhaps via its effects on edema.


Sertraline. Sertraline might be beneficial, acting via peripheral serotonin receptors in the gastrointestinal tract, reducing abnormal esophageal, gastric, or diaphragmatic mobility, or through more central effects on the hiccup reflex arc.

Medication combinations. Medication combinations have been reported as successful in ameliorating hiccups. Baclofen and gabapentin have each been shown to be useful in conjunction with omeprazole and cisapride, and the use of all 4 medications has also been helpful.³ However, cisapride is no longer available owing to its serious side effects. The benefit of using multiple medications must always be balanced against the potential side effects, particularly in a patient population with a

large burden of illness who already frequently take a number of other medications.

George is already using omeprazole. He is started on metoclopramide subcutaneously. Initially this seemed to be effective. But George continues to have bouts of bothersome hiccups. Baclofen, 10 mg orally 4 times daily, is added after ensuring adequate renal function. By the following day George's hiccups are resolved; however, he is drowsy. The baclofen dose is gradually decreased until the optimal dose is found.

Conclusion

Hiccups are common in health and illness. Simple non-pharmacologic techniques are often effective. Persistent hiccups greatly affect quality of life and can be difficult to manage. As gastrointestinal causes are common, metoclopramide and proton pump inhibitors should be attempted early on. If they are ineffective and renal function is adequate, baclofen seems most likely to be helpful. If renal function is impaired, chlorpromazine or haloperidol might be attempted (if this is the case, metoclopramide should be discontinued). Gabapentin can be useful alone or as add-on therapy. Reducing the frequency of recurrent or persistent hiccups is important, as it will improve overall quality of life. 

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Competing interests

None declared

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