

Drug Therapy of Hiccups

Drug	Regimen	Level of Evidence	Comments
Antidopaminergic agents: Dopamine blockade may suppress the hiccup impulse. ¹			
Chlorpromazine (<i>Thorazine</i>)	25-50 mg PO tid to qid. If symptoms persist for 2-3 days, give 25-50 mg IM. If still symptomatic, give slow IV infusion of 25-40 mg in 500-1000 mL saline to supine patient. Monitor blood pressure.	<ul style="list-style-type: none"> • Case series: Immediate relief without recurrence in 41 of 50 patients; relief with recurrence within 6 hours in 5 patients; no response in 4 patients.¹ • Other case reports of no response.¹ • Has been used to treat corticosteroid-induced hiccups⁸ and hiccups occurring during general anesthesia.¹⁵ 	<ul style="list-style-type: none"> • Considered first-line by one expert because it is FDA-labeled for intractable hiccups and had high success rate in large series of patients; cautions against chronic therapy due to tardive dyskinesia risk.¹ • Hepatotoxicity reported after hiccups treated with chlorpromazine plus valproate.¹⁵
Metoclopramide ¹ (<i>Reglan</i>)	5-10 mg IV/IM q8h, then 10-20 mg PO q6h. ¹	<ul style="list-style-type: none"> • Case series: 14 patients reported relief lasting 6-8 hours starting within 30 minutes of first IM/IV dose.¹ • Has been used to treat corticosteroid-induced hiccups⁸ and hiccups during general anesthesia.¹⁵ 	<ul style="list-style-type: none"> • May act on dopamine receptors in the GI tract to reduce strength of esophageal contractions, relax muscles in the stomach, and reduce gastric secretion.¹
Baclofen (<i>Lioresal</i>)	15 mg/day PO divided tid initially, increasing by 15 mg/day every 3 days up to a maximum of 75 mg/day. ²⁰ Maximum of 5 mg/day recommended for hemodialysis patients. ²¹	<ul style="list-style-type: none"> • Double-blind, randomized, crossover trial in 4 men who had not responded to chlorpromazine, diazepam, and metoclopramide. Baclofen did not terminate hiccups, but increased hiccup-free period by 69% with 15 mg/day and 120% with 30 mg/day.¹⁹ • Case series: Response rate of 71% in 14 patients when used alone in patients with no evidence of gastroesophageal disease.²⁰ 	<ul style="list-style-type: none"> • One expert considers it the drug of choice for intractable hiccups.¹⁵ • Do not discontinue abruptly; gradual tapering is recommended.¹⁶ • Renally excreted; CNS toxicity (encephalopathy and respiratory depression) reported in patients with end-stage renal disease.^{22, 23}
Gabapentin (<i>Neurontin</i>) "add-on" therapy ^{4,5}	1200 mg/day PO.	<ul style="list-style-type: none"> • Case series: 1 of 10 responded and 2 improved when gabapentin was substituted for baclofen in patients who did not respond to triple therapy with cisapride, omeprazole, and baclofen.⁴ • Case series: 3 patients responded to cisapride, omeprazole, baclofen, plus gabapentin.⁵ • Case report: Decreased intensity, but did not terminate hiccups in 1 patient (dose not reported).³³ 	<ul style="list-style-type: none"> • Consider as a substitute in patients who are unresponsive to baclofen.

Drug Therapy For Hiccups

Lead author: Jill Allen, Pharm.D., BCPS

Background

Hiccups are a spasmodic contraction of the diaphragm that is caused by stimulation of any segment of the hiccup reflex arc. In the afferent arm of the arc, impulses are sent from the phrenic and vagus nerves and sympathetic chain to the hiccup center in the spinal cord. In turn, the hiccup center communicates with many areas in the brain, including the respiratory center, reticular formation, and hypothalamus. In the efferent arm of the arc, impulses are sent via phrenic nerves and motor neurons to muscles of the respiratory diaphragm and glottis.¹

Although short bouts of hiccups are common, persistent (lasting more than 48 hours) or intractable (lasting more than a month) hiccups are rare. The estimated incidence at a large tertiary medical center is seven cases per year.²⁸ Approximately 80% of cases occur in older men with medical disorders.² Hiccups can be caused by central nervous system lesions (eg, multiple sclerosis plaques or tumors), intra-thoracic or intra-abdominal irritation (eg, during surgery or by gastroesophageal reflux), or metabolic disorders (eg, uremia).^{1,3} Rarely, they are drug-related. Because persistent hiccups occur so infrequently, it is very difficult to study them and there are no evidence-based recommendations for treatment. Drug regimens for intractable hiccups are summarized in the table above.

Approach to drug therapy

If an underlying cause of persistent hiccups can be identified, treatment should be directed at alleviating that condition. For example, when gastroesophageal reflux is diagnosed in patients with persistent hiccups, treatment for reflux may resolve the hiccups.²⁰ There are two approaches to treatment of persistent hiccups. Patients may be given a trial of one medication after another until hiccups resolve. Alternatively, medications with different mechanisms of action might be given in combination. For instance, cisapride (to stimulate gastric emptying; no longer readily available in the U.S.) and a proton pump inhibitor (to reduce gastric acid) have been used in combination with baclofen or gabapentin. In theory, cisapride and a proton pump inhibitor might reduce input to the hiccup center from receptors in the GI tract, while baclofen or gabapentin reduces activity within the hiccup center itself.^{4,5} Baclofen is the only drug that has been studied in a randomized controlled trial. In a cross-over study in only four men, it reduced the frequency of hiccups, but did not terminate them in any patient.¹⁹

Approach to non-drug therapy

Drugs are usually reserved for the treatment of hiccups when physical remedies have failed. Physical methods for terminating hiccups include interrupting or stimulating respiration (eg, breath holding or the Valsalva maneuver), irritation of the nasopharynx (eg, swallowing dry granulated sugar), counter-irritation of the vagus nerve (eg, applying pressure to the eyeballs), disruption of the phrenic nerve (eg, phrenic nerve block), counter-irritation of the diaphragm (eg, pulling knees to chest), and relief of gastric distension (eg, induced vomiting).^{1,6} Acupuncture has been used successfully to treat persistent hiccups.³⁴

Drug-induced hiccups

Hiccups may be drug-related in rare cases. Causality can be difficult to assess because patients often have medical disorders that can cause hiccups. As a complication of cancer chemotherapy (eg, cisplatin and anthracyclines), hiccups occur primarily in men.^{7,16} They commonly occur during general anesthesia.¹⁵ The most frequently implicated therapeutic classes are the corticosteroids, benzodiazepines, and dopa-minergic agonists (including amantadine).^{9,14,15} Other therapeutic classes for which more than one agent has been implicated include: barbiturates; opiates; antibiotics (macrolides, quinolone, beta-lactam); anticonvulsants (ethosuximide, lamotrigine, oxcarbazepine); antivirals (cidofovir, delavirdine, ritonavir); triptans and dihydroergotamine; antidepressants (serotonin reuptake inhibitors, mirtazapine, and nefazodone);

cholinergic agents (pilocarpine and cevimeline); atypical antipsychotics (olanzapine and quetiapine); Class IB antiarrhythmics (mexiletine and tocainide); proton pump inhibitors; and nicotine.^{8-10,16}

In theory, corticosteroids and megestrol may induce hiccups by lowering the threshold for synaptic transmission in the midbrain.¹¹ Some agents could affect the hiccup center via effects on GABA transmission in the CNS (benzodiazepines, felbamate, flumazenil, gabapentin, tiagabine, topiramate, zaleplon, and zolpidem). Others may act within the GI tract. Nicotine may stimulate gastric receptors.¹⁸ One case of intractable hiccups was reported in a child with ceftriaxone-induced pseudolithiasis.¹² Another was related to an esophageal ulcer caused by doxycycline.¹³ But many other agents have no proposed mechanism, and hiccups could be attributed to them by chance: amiloride, amifostine, amphotericin, beta interferon, carisoprodol, choriogonadotropin, cyclosporine, doxapram, dronabinol, galantamine, leuprolide, loratadine, ondansetron, propofol, and riluzole.^{16, 17}