***Appendix Table 1: Pharmaceutical agents proposed for hiccup therapy, suggested mechanisms of action.***

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| --- | --- | --- | --- | --- |
| **Class of pharmaceutics** | **Specific drug** | **(Proposed) mechanism of action in hiccups, comments** | **Important side effects** |  |
| ***Gastroprokinetics*** | Metoclopramide | Dopamine D3 antagonism, serotonergic 5-HT4 agonism, parasympathomimetic activity | Dystonia, parkinsonian-like symptoms, tardive dyskinesia, galactorrhea | 46,71,190 |
|  | Cisapride | 5-HT4 dopamine receptor antagonist, facilitates gastric emptying: reduction of afferent input  | Cardiac arrhythmias (prolonged QT interval, contraindicated in patients with long-QT syndrome) | 191,192 |
| ***Calcium channel blockers*** | Nifedipine, Nimodipine | Influx antagonism at L-type calcium channels on pathologically depolarized pre- and postsynaptic structures of hiccup reflex arcNimodipine: better central nervous system permeabilization | Reflex tachycardia | 173,183 |
| ***Anticonvulsants*** | Valproic acid | Increases GABAergic effects | Transient GI a symptoms (anorexia, nausea, vomiting), sedation, ataxia, tremor, rash, alopecia, appetite stimulation, weight gain; alteration of hepatic function (elevation of hepatic transaminases) | 172 |
|  | Carbamazepine | Sodium channel blockade, general stabilization of membrane potential | Drowsiness, vertigo, ataxia, diplopia, blurred vision, nausea, vomiting, hematological toxicity, hypersensitivity reactions; acute intoxication can induce stupor, coma or respiratory depression | 181 |
|  | Phenytoin | Reduces post-titanic potentiation of diaphragm and intercostal muscles | Hypotension, arrhythmia, bradycardia, ataxia, tremor, nystagmus, dizziness, anaemia, osteomalazia, gingiva hyperplasia, hirsutism, lymphadenopathy, behavioral changes | 182 |
| ***Central muscle relaxants*** | Baclofen | Dopamine release reduction through GABAB receptor stimulation, modulation of lower esophageal sphincter tonus | Nausea, vomiting, fatigue, dizziness, respiratory depression, hypotonia, bradycardia, hypothermia; withdrawal symptoms | 193 |
| ***Proton pump inhibitors*** | Omeprazole | Reduces gastric acid production: reduction of afferent input | Nausea, abdominal pain, constipation, flatulence, diarrhea, subacute myopathies, arthralgia, headaches, skin rashes; CYP2C19 inhibition, CYP1A2 expression induction | 191 |
| ***Nonselective beta blockers*** | Carvedilol | Ameliorating effect on sympathetic nervous system irritation; effect shown on tardive hiccups only | Congestive heart failure, bradycardia, bradyarrhythmia, bronchospasm, fatigue, sleep disturbances, depression; may blunt recognition of hypoglycaemia | 187 |
| ***Antipsychotics*** | Chlorpromazine | D2 dopamine receptor blockade in the hypothalamus | Sedation, somnolence, dizziness, agitation, extrapyramidal symptoms, orthostatic hypotension, constipation, dry mouth, skin reactions, rash, photosensitivity, hyperglycaemia, galactorrhea, amenorrhea, weight gain | 6 |
|  | Haloperidol | Dopamine antagonism | Fatigue, cramps, muscle stiffness, adynamia, dyskinesia, restlessness, blood pressure alteration, neuroleptic syndrome, circulatory failure, ileus | 174 |
|  | Olanzapine | Antiserotonergic effect decreases phrenic motoneuron activity, D2 receptor antagonism | Extrapyramidal symptoms, diabetes mellitus, hypersalivation, fatigue, somnolence, weight gain | 175,176 |
| ***Antiparkinsonian medication*** | Amantadine | NMDA b receptor agonist, anticholinergic activity; effect only shown on patients with Parkinson's disease | Nausea, dizziness, restlessness, sleep disorders, concentration problems | 194,195 |
| ***Neurostimulants*** | Methyl-phenidate | Dopamine and norepinephrine reuptake inhibition; modulation of wakefulness level away from an "irritable zone" in the inspiratory center that responds erratically to stimuli  |  | 179,180 |
| ***Sodium channel blockers*** | Quinidine sulphate | Prolongation of the refractory period in the diaphragm and respiratory musculature, impulse block at the myonerval junction | Nausea, vomiting, diarrhea, chinidonismic syndrome with overdoses: visual and auditory dysfunction, nystagmus, tinnitus, confusion, headache | 196 |
|  | Procaine | Phrenic nervous blockade | Restlessness, dizziness, convulsions, respiratory failure, myocardial impairment, rash | 6 |
|  | Lidocaine | Decreases cellular neuronal excitability and ectopic discharges via depolarization inhibition of type C sensory neurons (sodium channel blockade), membrane-stabilizing effect | Cardiac arrhythmia, bronchospasm, nausea, restlessness, somnolence, cramps, coma | 184 |
| ***Analgesics, anaesthetics*** | Nefopam | Inhibition of synaptosomal neurotransmitter uptake, activation of descending pain-modulating pathways, muscle relaxation, structurally related to antihistamines and antiparkinsonian drugs |  | 178 |
|  | Diethyl ether | Instillation into nasal cavity, possibly inhibits hiccup reflex by activation of another |  | 136 |
|  | Ketamine | Stimulation of cortex, hippocampus, subcortical structures blocks hiccup center, the local anesthetic effect blocks peripheral afferences to the hiccup center |  | 197 |
| ***Benzodiazepines*** | Midazolam | GABA agonist, decreases neuronal excitability, may act as tonic depressant on striated muscle reflexes |  | 186 |
| ***Tricyclic antidepressants*** | Amitriptyline | Low doses: synchronizing and general sedative effects |  | 188 |
| ***SSRIs*** | Sertraline | Possible reduction of abnormal GI a or diaphragmatic mobility via 5-HT4 receptors; stimulation of central autonomous 5-HT1A /5-HT2 receptors may cause inhibition of the hiccup reflex arc |  | 189 |
| ***Sympathomymetics*** | Ephedrine | Unknown; possibly bronchodilatation, nasal decongestant or central stimulation |  | 198 |
| ***Parasympatholytics*** | Atropine | Decreases intraesophageal pressure, sympathetic stimulation |  | 139 |
| ***Corticosteroids*** | Dexamethasone | Unknown; shown in a patient with AIDS c and PML d |  | 199 |
| ***Other*** | Marijuana | Not addressed |  | 200 |
| ***Anxiolytics*** | Tandospirone | 5-HT1A agonist, direct inhibitory effects on phrenic nerve activity via 5-HT1A receptors located in the medulla, may have inhibitory effect on diaphragmatic spasms |  | 201 |
| ***GABA analogues*** | Gabapentin | Modulation at α2δ subunit of voltage dependent calcium channels in the CNS; may cause enhancement of GABAergic inhibition on inspiratory musculature |  | 202-204 |

*a gastrointestinal*

*b N-methyl-D-aspartate*

*c acquired immunodeficiency syndrome*

*d progressive multifocal leukoencephalopathy*