



# Benzodiazepine-Induced Hiccups in Three Patients with Down Syndrome and Catatonia



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## Background

Singultus, commonly known as hiccups, is the sudden onset of erratic diaphragmatic and intercostal muscle contraction immediately followed by laryngeal closure. It ranges from acute bouts lasting minutes to intractable episodes lasting months, with a variety of etiologies reported in the literature.

The pathophysiology of hiccups is poorly understood but thought to involve a **dopamine** and **GABA-mediated** peripheral and central nervous reflex arc, causing enhanced phrenic nerve motor activity. Medications used to treat hiccups, including antipsychotics and benzodiazepines, can induce hiccups in some individuals. Catatonia is typically treated with benzodiazepines, however, the frequency of benzodiazepine-induced hiccups in patients with catatonia is unknown.

## Case Histories:

Three adult male patients with Down Syndrome and catatonia were treated with low dose lorazepam (<3mg). Each patient developed persistent hiccups that caused distress and disrupted sleep. Two patients had marked improvement of catatonia symptoms, while the third had equivocal response. Lorazepam was discontinued and hiccups resolved in all patients, but symptoms of catatonia persisted.

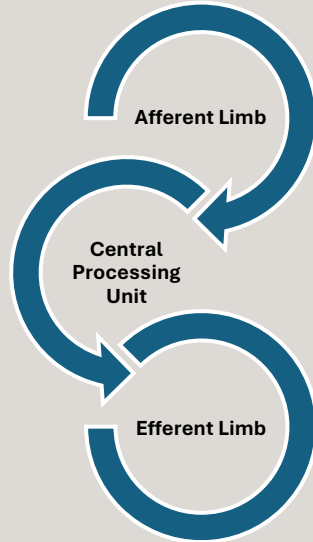
**Patient #1** - Retrial of lorazepam, starting at a lower initial dose with slow titration to higher dosing, was successful with significant improvement of catatonia and without recurrence of hiccups.

**Patient #2** - Developed recurrence of hiccups with both lorazepam and clonazepam, and unable to continue medication despite initial robust catatonia response.

**Patient #3** - Not re-trialed on lorazepam due to unclear initial benefit for catatonia, though never received higher, potentially more therapeutic lorazepam dosing.

## Pathophysiology of Hiccups

The exact mechanism of hiccups is complex and not fully understood. The function of hiccups is thought to be protective, with sudden closure of the glottis preventing hyperventilation.



## Hiccup Reflex Arc

Hiccups are mediated by a reflex arc consisting of three phases:

- **Afferent Limb** – Phrenic, Vagus, and Thoracic sympathetic nerve somatic and visceral sensory signals
- **Central Processing Unit** – Midbrain: Medulla oblongata, hypothalamus, chemoreceptors in the periaqueductal grey, subthalamic nuclei
- **Efferent Limb** – Phrenic nerve motor fibers to diaphragm and intercostal muscles - efferent motor fibers in the Vagus nerve cause sudden closure of the glottis

## Neurotransmitters Involved in Reflex Arc

Based on medications that are known to induce and treat hiccups, both central and peripheral neurotransmitters are thought to contribute to the reflex arc: dopamine, GABA, serotonin, glutamate, glycine, epinephrine, norepinephrine, acetylcholine and histamine.

## Discussion

Benzodiazepine-induced hiccups are rarely reported in the medical literature. In a clinic of individuals with Down Syndrome and catatonia, we identified three patients with paradoxical hiccup response to benzodiazepines. Intractable and intolerable hiccups caused by benzodiazepines can limit treatment options in this population, especially as the accessibility of Electroconvulsive Therapy may be limited.

## Conclusion

This case series illustrates the difficulty in treating catatonia when debilitating side effects occur with benzodiazepines. There is evidence of increased catatonia in individuals with Down Syndrome, and this case series suggests possible increased risk of benzodiazepine-induced hiccups in this population. Further study is warranted to examine potential shared underlying mechanisms, and consideration of alternative treatment options.

## Acknowledgments

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Conflicts of Interest: None

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