Autonomic-Type Symptom Burden in Benzodiazepine Withdrawal

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Dysautonomia International 14th Annual Conference

BACKGROUND

- Benzodiazepine withdrawal is clinically heterogeneous and may include cardiovascular/orthostatic, gastrointestinal/visceral, respiratory, thermoregulatory, sensory, affective, cognitive, and motor symptoms.
- Autonomic-type symptoms are commonly reported, but their distribution and co-occurrence within broader withdrawal presentations have not been well characterized.
- This exploratory analysis examined whether severe autonomic-type symptoms were diffusely distributed across the cohort or concentrated in a subset of patients with broader, overlapping multisystem symptom burden.

OBJECTIVE

To characterize the distribution and co-occurrence of severe autonomic-type symptoms in a cohort of patients experiencing benzodiazepine withdrawal, and to determine whether these symptoms were concentrated in a subset of patients with broader multisystem symptom burden.

METHODS

- **Participants:**
  Baseline observational data from **39 patients** enrolled in a specialty benzodiazepine withdrawal program. 37 were actively tapering, 2 were post-taper.

  Measures:
  A 233-item patient-reported symptom questionnaire was administered, with each symptom rated from 0 to 10. Symptoms rated ≥7/10 were classified as severe.

- **Domain Mapping:**
  Symptoms were mapped a priori to five broad candidate regulatory-system domains:
  - Corticotropin-releasing hormone (CRH)/adrenergic
  - Excitatory–neuroinflammatory (ENI)
  - Autonomic
  - Basal ganglia–cerebellar (BG/Cer)
  - Mast-cell activation syndrome overlap (MCAS-overlap)

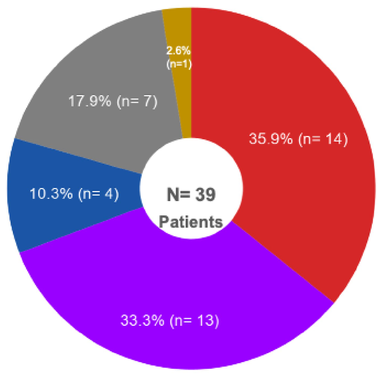
- **Autonomic analysis:**
  Representative autonomic symptom constructs were examined to characterize the distribution and co-occurrence of severe autonomic-type symptoms across patients. MCAS-overlap was defined as ≥2 MCAS-related symptoms rated ≥5/10 and was treated as a co-occurring modifier.
- **Study limitations:**
  Symptoms were patient-reported. Formal dysautonomia diagnoses, objective autonomic testing, mechanistic attribution, and causal inference were beyond the scope of this observational study.

RESULTS

- Four of 39 patients (10.3%) showed the highest severe autonomic-type symptom burden under the prespecified rule-based domain-scoring approach.
- Severe symptoms in these patients spanned cardiovascular/orthostatic, gastrointestinal/visceral, and respiratory domains.
- MCAS-overlap features were present in all four patients with high autonomic symptom burden.
- The autonomic pattern was multisystem, with severe symptoms distributed across several related body-regulation domains.

FIGURE 1 **Rule-Based Symptom Pattern Distribution**

Patients assigned to rule-based symptom patterns using severe symptom ratings (≥7/10), N = 39



CRH-heavy symptom pattern
35.9% (n=14)
Highest CRH/adrenergic symptom burden
(e.g. panic, intrusive thoughts, sleep disruption)

ENI symptom pattern
33.3% (n=13)
Highest ENI symptom burden
(e.g. pain, paresthesia, sensory disturbances, perceived neuroinflammation)

Autonomic symptom pattern
10.3% (n=4)
Highest autonomic symptom burden
(e.g. tachycardia, GI/visceral, respiratory burden)

Low-Symptom pattern
17.9% (n=7)
Lower overall symptom burden

Mixed pattern
2.6% (n=1)
Tie across ≥2 domain groupings

Most patients were assigned to one of three rule-based symptom patterns*: CRH-heavy, ENI, or Autonomic.*

Pattern assignments were based on the predefined symptom-domain grouping with the highest number of severe symptoms (≥7/10). These categories are descriptive and hypothesis-generating.

FIGURE 2 **Severe Autonomic-Type Symptoms Across Rule-Based Symptom Patterns**

Heat map of severe autonomic-type symptoms (≥7/10) by rule based symptom pattern.
Values show % of patients within each pattern reporting each severe symptom.

Autonomic type symptom construct (Severe ≥7/10)	CRH-heavy pattern (n=14, 35.9%)	ENI-heavy pattern (n=13, 33.3%)	Autonomic-high pattern (n=4, 10.3%)	Lower—symptom pattern (n=7, 17.9%)
Blood Pressure Instability	21%	15%	50%	0%
Dizziness	0%	15%	0%	0%
POTS/POTS-like (self-reported)	0%	8%	25%	0%
Palpitations	7%	15%	50%	0%
Tachycardia	29%	31%	25%	0%
Abdominal Cramping & Distention	0%	31%	50%	0%
Constipation	0%	31%	50%	0%
Dyspepsia	0%	23%	75%	0%
Nausea	21%	15%	50%	0%
Air Hunger	7%	23%	25%	0%
Chest Tightness	14%	15%	25%	0%
Dyspnea	7%	15%	25%	0%
Heat / Cold Intolerance	14%	15%	0%	0%
Temperature Fluctuations	21%	46%	0%	0%

% of patients with severe symptoms (≥7/10)
0-19% 20-39% 40-59% 60-79% 80-100%

Values represent the percentage of patients within each rule-based symptom pattern reporting each severe symptom (≥7/10). Pattern assignment was based on the predefined symptom-domain grouping with the highest number of severe symptoms. Mixed pattern excluded from heat map because n=1.

KEY FINDING

- Four of 39 patients (10.3%) showed concentrated severe autonomic-type symptom burden under the prespecified domain-scoring approach.
- Their symptoms spanned cardiovascular/orthostatic, gastrointestinal/visceral, and respiratory domains.
- MCAS-overlap features were present in all four patients with high autonomic symptom burden.
- The pattern was multisystem, with autonomic symptoms occurring across several related body-regulation domains.

FIGURE 3 **Clinical Profile of High Autonomic Symptom Burden**

n= 4 patients (10.3% of cohort) with the highest autonomic-domain severe symptom burden (≥7/10)

Domain	Severe Symptoms in Patients With High Autonomic Burden	Count n= 4	% of High Autonomic Group
Cardiovascular / Orthostatic	BP instability ≥7 Palpitations ≥7	2 / 4 2 / 4	50% 50%
GI / Visceral	Constipation ≥7 Dyspepsia ≥7	2 / 4 3 / 4	50% 75%
Respiratory	Air hunger ≥7 Dyspnea ≥7	1 / 4 1 / 4	25% 25%
MCAS-overlap	MCAS-overlap present	4 / 4	100%

Key Point: Patients with high autonomic symptom burden showed severe symptoms across cardiovascular/orthostatic, GI/visceral, respiratory, and MCAS-overlap domains.

Note: Pattern assignment reflects the symptom-domain grouping with the highest number of severe symptoms (≥7/10).

FIGURE 4: **MCAS-OVERLAP**

MCAS-overlap features were most frequent in the high-autonomic group

Overall, 53.8% of patients met the predefined MCAS-overlap symptom criterion. This was coded as a symptom-based modifier, not as a formal MCAS diagnosis.

INTERPRETATION/CONCLUSIONS

- **Concentrated autonomic burden:** Symptom mapping identified a small subgroup with concentrated autonomic symptom burden.
- **Multisystem autonomic pattern:** Severe symptoms spanned cardiovascular/orthostatic, gastrointestinal/visceral, and respiratory domains.
- **Clinical application:** Domain-based symptom mapping may help clinicians recognize when autonomic symptoms form a major component of a patient's overall withdrawal presentation.
- **Future directions:** Compare symptom-derived autonomic burden with objective autonomic testing and longitudinal symptom trajectories.

CONTACT / DISCLOSURES/PREPRINT

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Disclosures:
No commercial support for this research. No relevant ownership or financial interests to disclose.

Preprint:
Madhava V. Benzodiazepine Withdrawal Symptom Clusters: Distinct Phenotypes with Treatment Implications.
DOI:10.1101/2025.10.07.25336923

Note: This poster was updated in late July 2026 to reflect our current interpretation of the data, which emphasizes overlapping symptom organization rather than discrete phenotypes.