ISSN: 2690-909X

Research Article

Advances in Neurology and Neuroscience

Multifactorial Secondary Autonomic Dysfunction (MSAD) A Clinical Framework, Diagnostic Model, and Applied Assessment Tool in Autonomic Medicine

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Submitted: 2026, Jun 01; **Accepted:** 2026, Jun 22; **Published:** 2026, Jul 02

Citation: Knox, B. H. (2026). Multifactorial Secondary Autonomic Dysfunction (MSAD) A Clinical Framework, Diagnostic Model, and Applied Assessment Tool in Autonomic Medicine. *Adv Neur Sci, 9*(3), 01-05.

Abstract

Dysautonomia encompasses a spectrum of disorders characterised by impairment of autonomic nervous system (ANS) regulation across cardiovascular, gastrointestinal, thermoregulatory, genitourinary, endocrine, metabolic, cognitive, and sleep-related domains [1-6]. Current clinical frameworks distinguish between primary autonomic disorders and secondary forms arising from identifiable causes. However, increasing clinical observation suggests that some patients develop autonomic dysfunction through the cumulative effects of multiple physiological insults rather than a single disease process [5,6,21]. This monograph proposes Multifactorial Secondary Autonomic Dysfunction (MSAD) as an integrative clinical framework, combining a theoretical model of cumulative autonomic injury, a sequential diagnostic assessment framework, and an applied clinical scoring tool that translates theory into structured practice. MSAD is presented not as a replacement for established autonomic diagnoses, but as a bridging framework for complex multisystem presentations that are currently underserved by single-cause models

1. Introduction

The autonomic nervous system regulates multiple physiological systems, including cardiovascular control, gastrointestinal motility, thermoregulation, sweating, pupillary responses, bladder function, sexual function, endocrine interactions, metabolic regulation, and sleep-wake cycling [1,9,21]. Because autonomic fibres influence nearly every organ system, autonomic dysfunction may present with orthostatic intolerance, syncope, tachycardia, gastrointestinal dysmotility, urinary dysfunction, sexual dysfunction, sweating abnormalities, thermoregulatory disturbance, fatigue, sleep disruption, and cognitive impairment [14,19-21]. Patients frequently present across multiple medical specialties before autonomic dysfunction is recognised as the unifying process [17,18]. Traditional diagnostic approaches favour single-cause explanations. Yet many patients present with trajectories suggesting cumulative physiological stress and injury rather than one dominant pathology. MSAD provides a framework for recognising when cumulative burden exceeds physiological reserve.

2. Conceptual Framework: Cumulative Autonomic Injury

The central hypothesis of MSAD is that autonomic dysfunction may arise when multiple individually tolerable physiological insults collectively exceed the adaptive capacity of the autonomic nervous system. Potential contributors include viral illness, surgery, autoimmune activation, metabolic disease, nutritional deficiency, medication toxicity, trauma, chronic physiological stress, and age-related loss of reserve [3,5-7,12,13,21]. Individually, these factors may produce modest impairment. Collectively, their effects may become additive or synergistic, producing dysfunction greater than any single insult alone [5,6,21].

3. Clinical Characteristics of MSAD

- Multiple contributing insults are frequently identifiable, commonly involving three or more recognised autonomic stressors or injuries [30].
- Symptoms often accumulate progressively over months or years as physiological reserve becomes depleted [5,21].
- Patients frequently demonstrate multisystem involvement, including cardiovascular instability, heart-rate dysregulation, gastrointestinal dysmotility, bladder dysfunction, sexual dysfunction, thermoregulatory impairment, sweating abnormalities, sleep disturbance, fatigue, and cognitive impairment [2,4,9-11,14,21,26,27].
- No single diagnosis adequately explains the breadth, severity, or chronological development of the presentation [17,18,30].

- Delayed recognition is common because clinical findings are often distributed across cardiology, neurology, gastroenterology, endocrinology, rheumatology, urology, and rehabilitation medicine [17,18,21].

4. Sequential Diagnostic Assessment Framework

The proposed framework uses six sequential stages. It begins with objective confirmation of autonomic dysfunction, then evaluates multidomain involvement, cumulative insults, exclusion of alternative diagnoses, chronological coherence, and longitudinal trajectory.

Stage	Core question	Key components	Clinical interpretation
Stage 1	Does objective autonomic dysfunction exist?	Orthostatic hypotension or intolerance; abnormal heart-rate responses; baroreflex dysfunction; sudomotor abnormalities; abnormal tilt-table or active stand testing.	Confirms physiological dysfunction and guards against premature diagnostic attribution.
Stage 2	Are multiple autonomic domains involved?	Cardiovascular, gastrointestinal, thermoregulatory, sudomotor, genitourinary, sexual, cognitive, sleep, and exercise-tolerance domains.	Three or more domains increase suspicion; five or more strongly support a multisystem autonomic process.
Stage 3	Are multiple physiological insults present?	Viral illness, surgery, critical illness, autoimmune or inflammatory disease, metabolic disorder, nutritional deficiency, medication burden, trauma, chronic stress, and ageing.	Three or more factors suggest significant cumulative burden; five or more suggest high burden.
Stage 4	Can a single diagnosis explain the presentation?	Evaluation for MSA, PAF, AAG, hereditary dysautonomia, diabetes, medication effects, and other primary or single-cause disorders.	MSAD should be considered only after recognised disorders and simpler explanations have been appropriately evaluated.
Stage 5	Does chronology support cumulative injury?	Prior baseline function; symptoms after identifiable insult; worsening after additional insults; accumulation across time; coherent biological sequence.	Chronology may provide the strongest diagnostic signal for cumulative autonomic injury.
Stage 6	What does the longitudinal trajectory suggest?	Improved orthostatic tolerance, exercise capacity, sweating, thermoregulation, gastrointestinal function, bladder function, cognition, and reduced instability.	Improvement or fluctuation may suggest recovery, adaptation, or recalibration rather than steady neurodegenerative progression.

Table 1: Sequential Diagnostic Assessment Framework for MSAD

5. Translating Theory into Practice: The MSAD Clinical Scoring Tool

The MSAD Clinical Scoring Tool operationalises the framework by converting conceptual domains into a structured clinical checklist. It is intended to assist clinicians in recognising the pattern of cumulative, multisystem autonomic dysfunction; it does not replace formal autonomic testing or established diagnostic criteria for recognized autonomic disorders. The data in the table and chart illustrate the scores assigned to various components of autonomic dysfunction, emphasizing the severity of each element. These scores are subsequently aggregated to facilitate the ensuing interpretation.

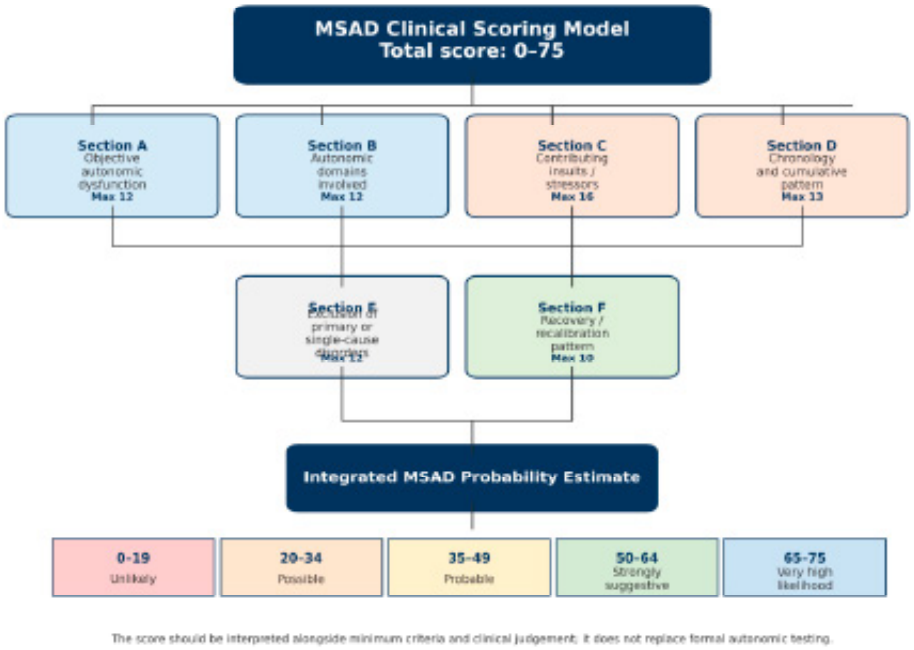

Figure 1: MSAD Clinical Scoring Tool conceptual model. The model integrates objective dysfunction, autonomic domains involved, cumulative insults, chronology, exclusion of alternatives, and recovery pattern to produce a total score out of 75.

The scoring system contains six sections: objective autonomic dysfunction; autonomic domains involved; identifiable autonomic insults or stressors; chronology and cumulative pattern; exclusion of primary or single-cause disorders; and recovery, recalibration, or non-progressive pattern.

5.1 Score Interpretation

Total score	Interpretation
0–19	MSAD unlikely. Consider alternative or single-system diagnosis.
20–34	Possible MSAD. Further history, autonomic testing, and specialist review recommended.
35–49	Probable MSAD. Multisystem dysfunction and cumulative burden are clinically significant.
50–64	Strongly suggestive of MSAD. Consider integrated autonomic management plan.
65–75	Very high likelihood MSAD phenotype. Suitable for specialist review, longitudinal monitoring, and possible research classification.

5.2. Minimum Criteria for Probable MSAD

- Objective autonomic dysfunction is present.
- Three or more autonomic domains are involved.
- Three or more plausible autonomic insults or stressors are identifiable.
- Chronology supports cumulative injury.
- No single diagnosis fully explains the presentation.

6. Recovery, Adaptation, and Recalibration

One important distinction between MSAD and primary neurodegenerative autonomic disorders is the possibility of meaningful recovery [8,22,29]. Several mechanisms may contribute, including neural adaptation, peripheral small-fibre regeneration, reduction of physiological stressors, and central autonomic recalibration [16,20,22,24,25]. Clinical improvement may become evident through improved orthostatic tolerance, increased exercise capacity, restoration of sweating, improved thermoregulation, better gastrointestinal or bladder function, improved sleep, enhanced cognition, and increased resilience to physiological stress [11,14,21,22,26,27,29]. Recovery is rarely linear. Periods of improvement may alternate with plateaus and temporary setbacks, but meaningful recovery may be possible in appropriately selected patients [22,28,29].

7. Diagnostic Challenges and Systemic Bias

MSAD remains under-recognised because it lacks formal classification, crosses specialty boundaries, and challenges the single-cause paradigm that continues to shape diagnostic reasoning [18,21,30]. Autonomic testing can demonstrate cardiovagal, adrenergic, sudomotor, orthostatic, and baroreflex abnormalities, but it rarely answers the question of causation [18,23]. Severe autonomic dysfunction may be interpreted through a neurodegenerative lens, particularly because disorders such as Multiple System Atrophy, Parkinson disease, and Pure Autonomic Failure have heavily influenced autonomic medicine [8,21]. However, severity and irreversibility are not synonymous. Profound dysfunction may occur in post-infectious, autoimmune, inflammatory, surgical, trauma-related, metabolic, and medication-

related contexts, some of which retain recovery potential [3,5,7,11,21,22,28,29].

8. The Role of Chronology and Patient Narrative

In MSAD, the patient narrative may provide crucial diagnostic coherence. The sequence of infection, injury, surgery, physiological stress, deterioration, stabilisation, and recovery may reveal cumulative causation more clearly than isolated test results. This does not diminish the value of objective testing. Rather, it places testing within a longitudinal biological narrative, allowing the clinician to distinguish isolated disease labels from cumulative network dysfunction.

9. Clinical Implications

Clinicians should consider whether multiple autonomic insults have accumulated over time, whether symptoms involve multiple autonomic domains, whether a single diagnosis adequately explains the presentation, and whether recovery potential differs from that expected in neurodegenerative disease. Management should focus on identification and treatment of contributing factors, reduction of ongoing autonomic stressors, optimisation of physiological repair processes, rehabilitation support, and longitudinal monitoring.

10. Future Directions

- Determine whether MSAD represents a distinct clinical entity or a descriptive framework.
- Estimate the prevalence of cumulative autonomic injury.
- Identify thresholds beyond which multiple insults produce network failure.
- Develop biomarkers for cumulative autonomic burden and autonomic reserve.
- Validate the scoring tool prospectively.
- Clarify predictors of recovery, fluctuation, and progression.

11. Conclusion

Multifactorial Secondary Autonomic Dysfunction provides a coherent and biologically plausible framework for understanding complex autonomic presentations arising through cumulative injury rather than a single identifiable disease process. The integration of a conceptual model, sequential diagnostic assessment framework, and applied scoring tool allows MSAD to move from theory toward clinical utility and future validation. The strongest diagnostic signal is not any single symptom, test, or insult, but the convergence of objective dysfunction, multisystem involvement, cumulative physiological burden, coherent chronology, exclusion of simpler explanations, and a potentially recoverable trajectory.

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