ORIGINAL ARTICLE

# Assessment of Dysautonomia (Autonomic Dysfunction) in Patients of GAD: A Cross-sectional Study

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## Abstract

**Background:** Generalized anxiety disorder (GAD) is a chronic and disabling psychiatric condition associated with increased autonomic dysfunction and cardiovascular risk. Autonomic dysfunction, characterized by dysregulation of the autonomic nervous system, is increasingly recognized as a key factor in GAD pathophysiology. This study aimed to assess autonomic dysfunction in GAD patients using the Composite Autonomic Symptom Score (COMPASS-31).

**Materials and methods:** A cross-sectional study was conducted during the month of December 2024 at ICARE Institute of Medical Sciences and Research and Dr Bidhan Chandra Roy Hospital, Haldia. The study included 100 participants (50 GAD patients and 50 healthy controls) aged 18–45 years. The GAD diagnosis was based on International Classification of Diseases, Tenth Revision criteria. Autonomic dysfunction was assessed using COMPASS-31, and anxiety severity was evaluated using the GAD-7 scale. Data were analyzed using Statistical Package for Social Sciences, with statistical significance set at $p < 0.05$.

**Results:** The GAD patients exhibited significantly higher COMPASS-31 scores (27.84 ± 7.02) compared with healthy controls (9.12 ± 4.64, $p < 0.01$). The orthostatic domain showed the highest score among GAD patients (10.82 ± 4.02, $p < 0.01$), followed by gastrointestinal dysfunction (7.96 ± 3.44, $p < 0.02$). Elevated systolic and diastolic blood pressures were observed in GAD patients (126.12 ± 6.02 mm Hg and 84.06 ± 9.58 mm Hg, respectively) compared with controls. Regression analysis revealed a positive correlation between GAD severity and COMPASS-31 scores, with moderate-to-severe GAD significantly associated with higher autonomic dysfunction scores.

**Conclusion:** This study highlights significant autonomic dysfunction in GAD patients, emphasizing the role of the autonomic nervous system in GAD pathophysiology. The COMPASS-31 questionnaire proved to be a useful screening tool for autonomic dysfunction in this population. Future research should explore interventions targeting autonomic regulation to improve clinical outcomes in GAD.

**Keywords:** Autonomic dysfunction, Autonomic nervous system, Composite autonomic symptom score-31, Dysautonomia, Generalized anxiety disorder.

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## Introduction

Generalized anxiety disorder (GAD) is a widespread and debilitating condition that is frequently misdiagnosed and undertreated. Patients with GAD are at a greater risk of suicide, cardiovascular-related complications, and death.[1]

According to International Classification of Diseases, Tenth Revision (ICD-10), the core feature of GAD is anxiety, which is pervasive and ongoing but not restricted to or even substantially predominates in any particular environmental circumstances. Although its route is unpredictable, it usually takes a long time. For at least weeks, and typically for several months, the patients must experience their primary anxiety symptoms on most days. The following symptoms were usually observed:

- Apprehension: Fears about potential misfortunes, feeling "on edge," and difficulty concentrating.
- Motor tension symptoms include fidgeting, headaches, shaking, and difficulty relaxing.
- Symptoms of autonomic overactivity include light-headedness, sweating, tachycardia, tachypnoea, epigastric pain, dizziness, and dry mouth.[2]

An anomaly in the autonomic nerve system's operation is called dysautonomia. There are typically two types: parasympathetic and sympathetic. The most noticeable symptoms of dysautonomic disorders are produced by aberrant sympathetic division function out of these two systems.[3] An elevated risk of abrupt cardiac arrest is often associated with sympathovagal imbalance. Cardiovascular reflex testing and heart rate variability (HRV) are noninvasive, sensitive, and quantitative methods that indicate the autonomic nervous system's dynamic nature.[3,4]

There is no one illness mechanism that causes dysautonomia. Numerous degenerative neurologic disorders can cause damage to the autonomic nervous system. These are called as Primary

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Dysautonomia. Injuries to the autonomic nervous system can also arise and become a major component of non-neurologic systemic disorders of many sources. Those are again called as Secondary Dysautonomia. Lastly, an Iatrogenic Type of Dysautonomia is frequently caused by pharmacological side effects that present as anomalies in the autonomic nerve system's function. The reasons of dysautonomia are numerous.[5]

Dysautonomia usually presented in different psychiatric disorders, e.g., mood-related disorders (major depressive disorder, bipolar disorder), anxiety disorders (panic, GAD, social anxiety, post-traumatic stress disorder, phobia), obsessive compulsive disorder, psychotic disorders (schizophrenia, schizoaffective disorder, schizophreniform disorder), and substance-dependence disorders (alcohol, methamphetamine, opioid). Even dysautonomias may be because of treatment of different psychiatric conditions by antidepressants (serotonin–norepinephrine reuptake inhibitor, selective serotonin reuptake inhibitor, and tricyclic antidepressant) and antipsychotics (amisulpride, clozapine, olanzapine, and sertindole).[6]

Symptoms of dysautonomias:

- Postural hypotension can manifest as weakness, light-headedness, fainting, blurred vision, unsteady walking, slurred speech, and workout syncope.
- Urinary dysfunction, including stress incontinence, urgency, nocturia, and frequency.
- Sexual dysfunction, which includes dry or retrograde ejaculation, impotence, and loss of libido.
- Bowel dysfunction, which includes rectal incontinence, nocturnal diarrhea, and intermittent diarrhea.
- Less perspiration.[5]

Immune dysregulation, which is thought to be a key factor in the pathophysiological causes of GAD, has an impact on the kynurenine metabolic pathway.[7] At the same time, immunological dysregulation is thought to contribute to accelerated atherosclerosis.[8] Immune dysregulation may thereby impact cardiovascular and mental health, which is why GAD is referred to as a "neurocardiovascular" condition.

On this basis, a symptoms-based questionnaire that evaluates dysautonomia in depressed persons may prove to be a useful assessing instrument in general care. An authorized instrument for measuring autonomic dysfunction in patients with autonomic neuropathy, the Composite Autonomic Symptom Score (COMPASS)-31 is a condensed variety of the comprehensive 164-items COMPASS assessment questionnaire with 31 questions.[9]

## Materials and Methods

### Place, Period, and Population of the Study

This cross-sectional study was conducted during the month of December 2024 on healthy individuals and persons diagnosed with GADs as per ICD-10, attending the Outpatient Department (OPD) as well as admitted at Indoors of the Psychiatry Department in ICARE Institute of Medical Sciences and Research and Dr Bidhan Chandra Roy Hospital, Haldia.

### Ethical Considerations

This study was approved by the Ethical Committee of ICARE Institute of Medical Sciences and Research and Dr Bidhan Chandra Roy Hospital, Haldia.

The study obtained informed consent from all participants, ensuring their voluntary involvement.

### Sample Size

Approximately 5.8% of the Indian population aged 18 years and older suffer from GAD.[9]

The formula which is used to calculate sample size is

$$\text{Sample size} = \frac{Z_{1-\alpha/2}{}^2\, p\,(1-p)}{d^2}$$

with absolute error or precision 5%.[10,11]

In this way, for sampling for this study, researcher has to take at least 84 subjects.

So, we have taken 100 subjects (*N*) for this study. As they are divided equally into two groups, then each group will have 50 subjects.

### Sample Design

Among patients suffering from GADs, those who had fulfilled the inclusion criteria were allowed in study group and those who were not fulfilling the inclusion criteria had been excluded from the study. Healthy individuals from the hospital and family members were taken as controls.

### Selection of Controls

Case control was required, i.e., 50 healthy individuals.

The inclusion criteria for controls ensured that they were free from chronic medical illnesses, substance use disorders, cardiovascular and metabolic disorders, or pregnancy (for female participants). The careful selection of controls strengthens the validity of the findings by minimizing confounding factors that could influence autonomic function. Controls were selected from various family members of the patients' attending the OPD with consent.

### Inclusion Criteria

- Patients who were already diagnosed according to ICD-10 with GADs.
- Healthy individuals who matched regarding age and gender.
- Age-group: 18–45 years of all sex groups.

### Exclusion Criteria

- Any significant chronic medical illness/substance abuse/any chronic metabolic disorders/cardiovascular disorders/gastrointestinal disorders/any pregnant females.

### Study Variable

Sociodemographic variables, like age, sex, education, religion, locality, economic status, etc.

### Laboratory Investigations

No laboratory investigation was needed for caregivers. All reports of the patients had been collected if needed.

### Outcome Definition and Parameters

This study was done to assess the severity of dysautonomia using COMPASS-31 scores between patients with GAD and healthy controls.

### Study Tools

*Consent Form*

It was written in three languages: Bengali, Hindi, and English. At first, the informants, i.e., the patients had been enlightened about the aim of the study and were explained the whole procedure and the content of the consent form in their own language.

### *Case Record Form*

It was written in English. At first, the informant, i.e., the patients had been informed the purpose of the study. Then, patients were asked the questions related to the case, recorded, and noted.

It was a combination of different social and different demographic factors that define individuals in a particular group or population. It includes age, sex, education, religion, marital status, household, background, employment, income, etc.

### *Assessment Scales Like*

- Generalized Anxiety Disorders 7-items

It is a simple initial assessing test for generalized anxiety disorder, consisting of seven items.[12,13] The total score is 21. A reasonable cut-point for determining the probable cause of GAD is a score of 8 or higher. This GAD-7 items has sensitivity of 92% and specificity of 76% for diagnosing GAD when a cut-off of 8 is used.[14]

The following cut-off correlate with level of anxiety frequency.[15]

| *Score* | *Frequency* |
|---|---|
| 0–4 | Minimal anxiety |
| 5–9 | Mild anxiety |
| 10–14 | Moderate anxiety |
| >15 | Severe anxiety |

Based on a recent meta-analysis, several specialists advise thinking about utilizing a cut-off of 8 to maximize sensitivity without sacrificing specificity.[15]

- Composite Autonomic Symptom Score-31

These 31 questions on this scale are mostly related to six areas of sympathovagal imbalance: urine dysfunction, secretomotor abnormalities, pupillomotor disturbances, orthostatic dysfunctions, gastrointestinal dysfunction, vasomotor imbalance. If added together, the total score typically falls between 0 and 100. Orthostatic intolerance can have score of 40, followed by gastrointestinal dysfunction at 25, glandular abnormalities at 15, urinary ailments at 10, and vasomotor and pupillomotor issues at 5 each. The scale's internal validity of 0.9 is exceptional.[16] A COMPASS-31 score of 20 suggests moderate to severe autonomic dysfunction.[17,18]

- Data chart in Microsoft Excel.
- Statistical Package for Social Sciences (SPSS) software.

## Statistical Analysis

- Statistical analysis had been carried out according to standard analytical and interventional study protocols.
- Statistical test for descriptive study had been applied by SPSS version.
- Quantitative data would be expressed in mean ± standard deviation (SD), while qualitative factors were expressed in percentage (%).
- A *p*-value of less than 0.05 was deemed statistically significant.

# Results

In this study, the selected 100 participants completed the COMPASS-31 assessment tool. Table 1 displays statistics on vitals and demographic profile of the study sample. This study consisted of 50 GAD patients (mean age: 33.02 ± 9.12 years) and 50 healthy

**Table 1:** Sociodemographic attributes of 100 subjects

| | *Numbers (n) (total = 100)* | |
|---|---|---|
| | *GAD (50)* | *Controls (50)* |
| *Features* | *n/mean ± SD* | *n/mean ± SD* |
| Mean age (years) | 33.02 ± 9.12 ($p < 0.12$) | 30.84 ± 8.95 |
| Gender | | |
| Male | 26 | 24 |
| Female | 24 | 26 |
| Marital status | | |
| Single | 23 | 27 |
| Married | 19 | 16 |
| Divorced | 2 | 5 |
| Widowed | 4 | 4 |
| Education | | |
| Illiterate | 2 | 1 |
| Up to metric (10th) | 3 | 5 |
| Up to higher secondary (12th) | 23 | 20 |
| Graduation | 14 | 10 |
| Postgraduation | 4 | 7 |
| Professionals | 6 | 9 |
| Employment status | | |
| Employed | 18 | 14 |
| Unemployed | 10 | 13 |
| Business | 9 | 7 |
| Agricultural work | 6 | 6 |
| Housewife/household activity | 7 | 10 |
| Religion | | |
| Hindu | 29 | 33 |
| Muslim | 19 | 15 |
| Christian | 1 | 1 |
| Others | 1 | 1 |
| Locality | | |
| Rural | 25 | 23 |
| Urban | 25 | 27 |
| Economic background | | |
| Upper class | 10 | 11 |
| Middle class | 26 | 29 |
| Lower class | 14 | 10 |
| Mean disease duration of GAD (in years) | 2.84 ± 1.07 | 0 |
| Current status of the patients (with medication) | | |
| Manageable | 32 | 0 |
| Partially manageable | 13 | 0 |
| Not manageable | 5 | 0 |
| Systolic blood pressure | 126.12 ± 6.02 ($p < 0.01$) | 120.44 ± 8.92 ($p < 0.01$) |
| Diastolic blood pressure | 84.06 ± 9.58 ($p < 0.01$) | 76.48 ± 10.86 ($p < 0.01$) |

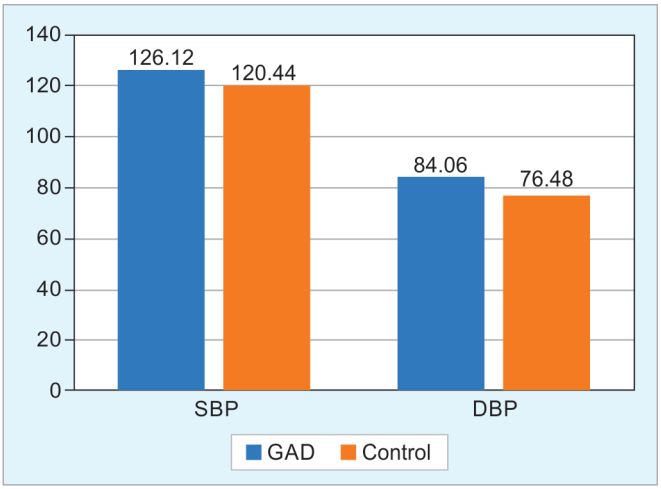


**Fig. 1:** Mean SBP and DBP ($p < 0.01$). SBP, systolic blood pressure; DBP, diastolic blood pressure

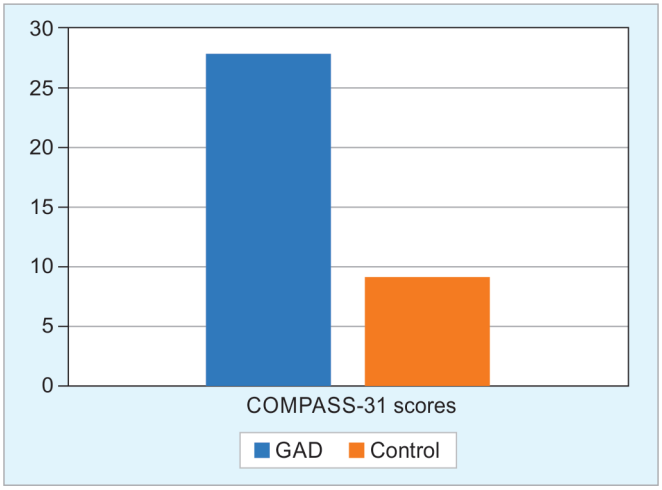


**Fig. 2:** A comparison of mean COMPASS-31 scores ($p < 0.01$)

controls (mean age: 30.84 ± 8.95 years), with not much significant differences in age. The patients and controls both groups had similar gender distributions, i.e., 52% (26) and 48% (24) males, respectively, as well as 48% (24) and 52% (26) females subsequently. Patients' mean disease duration was 2.84 ± 1.07 years. Most patients and controls were educated more or less, as per socioeconomic distribution between patients and control groups were kind of similar.

Notably, our results indicate that approximately 2.84 ± 1.07 of the GAD patients exhibited maximum manageable with medication 64% (64). Furthermore, our analysis revealed no significant intergroup differences in socioeconomic variables.

Table 1 presented significant differences in blood pressure and COMPASS-31 scores between patients with GAD and healthy controls. Specifically, GAD patients exhibited elevated systolic and diastolic blood pressures (126.12 ± 6.02 mm Hg and 84.06 ± 9.58 mm Hg, respectively) and is also shown in Figure 1.

A statistically significant between-group difference was observed in COMPASS-31 scores, with GAD patients exhibiting higher scores (27.84 ± 7.016, $p < 0.01$) than healthy controls (9.12 ± 4.64, $p < 0.01$), as shown in Figure 2.

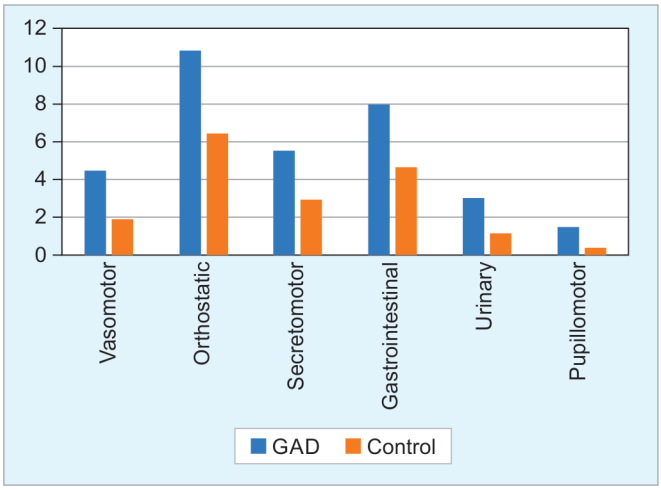


**Fig. 3:** Comparison of scores of all six subdomains of COMPASS-31

Further analysis on COMPASS-31 subdomains revealed marked differences between GAD patients and healthy controls, with orthostatic domain scoring highest (10.82 ± 4.02, $p < 0.01$), followed by the gastrointestinal domain (7.96 ± 3.44, $p < 0.02$), as illustrated in Figure 3.

Our linear regression analysis demonstrated a positive association between the severity of anxiety in GAD patients and COMPASS-31 scores. Notably, patients with moderate anxiety (score: 9–14) and severe anxiety ( score: ≥15) exhibited significantly more elevated COMPASS-31 scores than individuals with no or minimal (score: 0–4) depression, as shown in Table 2. In accordance with this, patients with mild GAD (scores: 5–9) exhibited significantly lower mean COMPASS-31 scores as compared with anxiety-free controls, as shown in Table 2.

Notably, the significant differences were robust to adjustments for age and sex, as evidenced by the adjusted odds ratio (OR) of 4.72 [95% confidence interval (CI): 2.32–8.84, $p < 0.02$]. Conversely, patients with GAD who exhibited partially manageable and nonmanageable with medications demonstrated elevated COMPASS-31 scores, which remained statistically significant following adjustment (OR: 3.24, 95% CI: 2.68–6.14, $p < 0.02$ and OR: 1.02, 95% CI: 0.52–2.24, $p < 0.03$, respectively), as presented in Table 2.

## Discussion

The COMPASS-31 questionnaire, a validated screening tool, was used in this study to estimate the degree of dysautonomia in GAD patients. The numerous pathophysiological processes of dysautonomia or autonomic dysregulation and their relationship to GAD have not received much attention up to this point, but autonomic dysfunction in GAD is a contentious issue.[19,20]

There is currently no gold standard test or precise data on the degree of dysautonomia and how it relates to GAD. In practice, heart rate variability and noninvasive autonomic function tests are typically utilized to treat sympathovagal imbalance in a variety of patient groups. Although the aforementioned tests have shown promise, their high cost and the knowledge needed to administer them have highlighted the need for a recognized screening tool to measure autonomic dysregulation symptoms.[21]

Measures of cardiac period variability were used to compare the autonomic features of distress and GAD in a study conducted a few years ago (in 1996). The resting baseline, relaxation, and

**Table 2:** Multivariate linear regression analysis between dependent variables and mean COMPASS-31 scores

| *Dependent variables* | *Unadjusted OR (95% CI)* | *p-value* | *Adjusted with age and sex, OR (95% CI)* | *p-value* |
|---|---|---|---|---|
| Severity of GAD (scores) | | | | |
| Minimal anxiety (0–4) | – | – | – | – |
| Mild anxiety (5–9) | 8.64 (4.52–11.78) | <0.01 | 4.72 (2.32–8.84) | <0.02 |
| Moderate anxiety (10–14) | 4.26 (2.06–8.22) | <0.01 | 2.94 (1.84–4.28) | <0.01 |
| Severe anxiety (≥15) | 2.42 (1.04–4.024) | <0.01 | 1.32 (0.94–2.86) | <0.02 |
| Manageability with medications | | | | |
| Partially manageable | 5.84 (2.44–8.68) | <0.01 | 3.24 (2.68–6.14) | <0.02 |
| Nonmanageable | 2.04 (0.88–4.04) | <0.02 | 1.02 (0.52–2.24) | <0.03 |

CI, confidence interval; OR, odds ratio

concern periods were used to record cardiorespiratory responses of 34 GAD patients and 32 nonanxious controls. The findings showed variations between baseline, relaxation, and distress periods, as well as between GAD patients and controls. Across all task circumstances, GAD customers showed reduced high frequency spectral power and shorter heart interbeat intervals (IBIs). Actual concern was linked to—(1) shorter IBIs, (2) decreased mean successive differences of the cardiac IBIs, and (3) decreased high frequency spectrum capability compared with baseline and relaxation conditions. These results imply that decreased cardiac vagal control is linked to GAD and its hallmark trait, concern. The results of this study support the need for more research on how autonomic nervous system activity contributes to GAD.[19]

According to recent research, autonomic hypersensitivity in GAD patients was demonstrated at modest adrenergic stimulation levels. This hypersensitivity was characterized by an accelerated heart rate, increased anxiety, increased bodily awareness, and a diminished neural response, i.e., localized to ventromedial prefrontal cortex (vmPFC). Individual who are suffering from distress or anxiety, can control sympathetic arousal signals associated with regulatory dysfunction in vmPFC more than normal individuals.[20]

Significant orthostatic intolerance and vasomotor abnormalities, which are signs of global dysautonomia, were observed in GAD patients in the current investigation. These results are in line with other research that used an orthostatic intolerance questionnaire to assess the relationships between depression and orthostatic intolerance.[22]

Additionally, there were severe gastrointestinal abnormalities observed in the depressed participants, which raises numbers of questions related to the interaction between the brain and gut. This primary link between the gut–brain axis, the vagus nerve, possibly directly stimulated to cause anxiety-like behavior in rats, according to a 2016 study. Some investigations or research had been done on probiotics and used as adjuvant therapy for few psychiatric diseases in line with the findings above.[23]

Global autonomic dysfunction was observed in these GAD patients in our investigation. This finding indicates that sudomotor dysfunction was consistent with earlier research that demonstrated that in a number of diseases or conditions involving central nervous system, the neuronal inflammations in dense autonomic fibers typically results in a loss of sudomotor control. As a result, an imbalance occurs in the central nervous system's thermoregulation system, which is identified by quantitative sudomotor axon reflex testing and thermoregulatory sweat testing.[24]

In accordance with this, the current study found that patients with GAD had pupillomotor impairment. Pupillomotor function has been considered to be moderately decreased in a number of diseases or conditions that affect both central and peripheral nervous systems, such as Parkinsonism and Alzheimer's disease. For this reason, additional research employing dynamic pupillometry is still required to evaluate these individuals' light reflexes and other reflexes.[25]

Here, the symptoms of urinary dysfunction that are also observed in patients with autonomic dysfunction, such as trouble urinating and loss of bladder control, are also noticed in GAD patients.[26] However, the exact origin of urinary symptoms is still unknown; it could be related to both the pathophysiology of GAD and autonomic dysfunction.[27–29]

The use of COMPASS-31, a validated questionnaire to measure global dysautonomia in favor of a single autonomic nerve system component is what makes our study sound.[30]

Research has consistently shown that GAD patients exhibit altered HRV and increased sympathetic activity, leading to cardiovascular and autonomic impairments. A study by Chalmers et al. highlighted that reduced HRV is a hallmark of anxiety disorders, reflecting an imbalance in autonomic control. Similarly, a study by Alvares et al. demonstrated that autonomic dysfunction is prevalent across psychiatric disorders and can be exacerbated by psychotropic medication use. The present study aligns with these findings by confirming significant autonomic symptoms in GAD patients. However, while previous studies predominantly relied on HRV and other physiological measures, this study is unique in utilizing the COMPASS-31 questionnaire, which provides a broader and more subjective assessment of autonomic symptoms.[6,31]

Several studies have explored the link between autonomic dysfunction and psychiatric conditions, with findings indicating that dysautonomia may contribute to heightened anxiety sensitivity. Research by Teed et al. demonstrated that autonomic hypersensitivity to adrenergic stimulation is a key feature of GAD, leading to increased heart rate, heightened bodily awareness, and regulatory dysfunction in the vmPFC.[32] A meta-analysis by Beauchaine and Thayer further supports the notion that autonomic nervous system dysregulation plays a significant role in anxiety pathophysiology, with evidence pointing toward hyperactivity in the sympathetic nervous system and inadequate parasympathetic counter-regulation. Our study supports these findings by showing elevated blood pressure and significant autonomic dysfunction in GAD patients.[33] Additionally, studies on the gut–brain axis, such as those by Cryan and Dinan and Foster et al., have suggested that gastrointestinal dysfunction plays a critical role in anxiety disorders, which aligns with our findings of significant gastrointestinal impairment in GAD patients.[34,35]

While past studies predominantly relied on HRV and other physiological tests, this study employs a validated self-reported measure to assess multiple domains of autonomic dysfunction in GAD.[22,24,27] Unlike earlier research that emphasized cardiovascular dysautonomia, this study provides a comprehensive assessment of autonomic dysfunction, including urinary, gastrointestinal, vasomotor, and pupillomotor impairment. This study suggests COMPASS-31 as a practical screening tool for autonomic dysfunction in GAD patients, making it accessible for primary care settings where objective autonomic testing may not be feasible.[21,24,27–30]

Nevertheless, instead of emphasizing the severity of sympathovagal imbalance, this COMPASS-31 questionnaire gauges the actuality of autonomic dysfunctions. A thorough assessment is recommended for GAD patients, incorporating reflex tests, Holter monitoring, and baroreflex sensitivity analysis. Additionally, identifying specific biomarkers can aid in early detection of dysautonomia. Initial screening with the COMPASS-31 scale can help guide this process.[36]

### Limitations

This study has limitations that provide a foundation for future research, notably the absence of in-depth qualitative assessments to explore the connection between autonomic dysfunction and the COMPASS-31 scale. Controls were not evaluated medically. Furthermore, the antidepressant medications taken by GAD patients were not analyzed separately, as most patients received combination therapy involving both tricyclic antidepressants and selective serotonin reuptake inhibitors.

## Conclusion

The study has yielded pertinent insights into the correlation between anxiety and different aspects of dysautonomia in GAD patients. Future investigations into the pathophysiological mechanisms behind depression-related dysautonomia are necessary. Primary care physicians can utilize the COMPASS-31, a validated self-reporting scale, to screen patients with depression for autonomic dysfunction. Treatment strategies should then prioritize addressing sympathovagal imbalance and targeting the nervous system.

### Author Contributions

Both the authors have reviewed and approved the final manuscript, taking full responsibility for the accuracy and integrity of the work. Concept and design; acquisition, analysis, or interpretation of data**;** drafting of the manuscript; and critical review of the manuscript for important intellectual content: Moumita Mandal and Chayan K Manna. Supervision: Chayan K Manna.

### Ethical Approval

The study received ethics approval from the Institutional Ethics Committee of ICARE Institute of Medical Sciences and Research and Dr Bidhan Chandra Roy Hospital, Haldia, West Bengal, India.

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