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Research Article

Non-Motor Symptoms in Gabapentin Users: A Clinical Evaluation

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ABSTRACT

Objective: Gabapentin is widely used for neuropathic pain, epilepsy, and other indications; however, its non-motor side effects remain understudied. This prospective, cross-sectional observational study aimed to evaluate non-motor symptoms in gabapentin users, assessed with the Non-Motor Symptom Scale (NMSS).

Methods: The Turkish version of the NMSS was administered once to 105 patients who had been receiving gabapentin for at least 120 days and to 107 demographically matched healthy controls at our Non-Motor Symptom Scale (NMSS) between January and December 2022. Exclusion criteria included neurodegenerative diseases, diabetes, psychiatric disorders, and thyroid dysfunction. Group comparisons were performed using independent samples t-tests for continuous variables and chi-square or Fisher's exact tests for categorical data.

Results: Gabapentin users had significantly higher total NMSS scores than controls (11.6 ± 5.56 vs. 6.03 ± 4.28, $P < 0.001$). Symptoms such as salivation, constipation, urgency, nocturia, pain, memory impairment, depression, anxiety, sexual dysfunction, orthostatic hypotension, daytime sleepiness, and leg edema were reported more frequently in the gabapentin group ($P < 0.05$).

Conclusion: Gabapentin use was associated with a higher frequency of non-motor symptoms, as assessed by the NMSS. This study suggests that the NMSS may serve as a structured tool for the systematic screening of non-motor symptoms in patients receiving gabapentin. Prospective studies with indication-matched controls and validated assessment tools are warranted to confirm these associations.

Keywords: Salivation, constipation, gabapentin, urinary incontinence, non-motor symptoms

INTRODUCTION

Gabapentin was first approved by the United States Food and Drug Administration in 1993 for the treatment of postherpetic neuralgia and epilepsy. The European Medicines Agency later approved the drug for the treatment of neuropathic pain. Beyond its approved indications, gabapentin is frequently prescribed off-label for migraine, trigeminal neuralgia, acute or chronic postoperative pain, relief of fibromyalgia symptoms, psychiatric disorders (such as anxiety and bipolar disorder), alcohol and opioid withdrawal syndromes, insomnia, restless legs syndrome (RLS), and pruritus associated with certain dermatological conditions.[1,2] Over the last decade, gabapentin prescriptions have quadrupled due to its broad indication profile and analgesic efficacy.[3] Correspondingly, reports of adverse effects—including sedation, dizziness, somnolence, ataxia, nystagmus, nausea, and vomiting—have increased.[4,5]

In our clinical practice, gabapentin-treated patients have reported subjective complaints such as hypersalivation, constipation, and sexual dysfunction. These symptoms are not routinely assessed in clinical practice. Although the Non-Motor Symptom Scale (NMSS) was originally developed for Parkinson's disease, we considered it the most structured and multidimensional tool available for systematically evaluating non-motor effects potentially associated with gabapentin use. The NMSS has also been applied in conditions such as idiopathic or isolated rapid eye movement (REM) sleep behavior

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disorder and essential tremor to explore non-motor domains beyond idiopathic Parkinson's disease.[6,7] However, to our knowledge, this is the first study employing the NMSS to assess medication-related non-motor adverse effects.

The NMSS provides a comprehensive assessment across multiple non-motor domains but evaluates only the presence of symptoms, not their severity. Although the NMSS was originally developed and validated for Parkinson's disease, we selected it for this study because gabapentin is known to affect several non-motor systems, including gastrointestinal, urinary, mood, and sleep functions. A structured tool capable of simultaneously screening a wide range of non-motor symptoms (NMS) was required; the NMSS was considered the most suitable instrument reported in the literature.

Gabapentin is widely used for neuropathic pain, epilepsy, and other indications, and is known to affect multiple non-motor domains, including gastrointestinal and urinary function, mood, and sleep. However, its non-motor side effects remain understudied and have not been systematically evaluated with structured instruments. Therefore, the aim of the present study was to assess NMS in patients using gabapentin, applying the NMSS as an exploratory screening tool.

MATERIAL AND METHODS

Patients aged 18-65 years who had been receiving gabapentin treatment for at least 120 consecutive days for various indications, including neuropathic pain, postherpetic neuralgia, and migraine prophylaxis, at the Mengücek Gazi Training and Research Hospital Neurology Outpatient Clinic between January 2022 and December 2022 were included in the study. Patients with incomplete clinical records, irregular medication use, or concurrent treatment with other anticonvulsants or antidepressants were excluded. Written informed consent was obtained from all participating patients, and the study protocol was approved by the Ethics Committee of Erzincan Binali Yıldırım University. Individuals with neurodegenerative or cardiovascular diseases, diabetes mellitus, primary gastrointestinal or genitourinary diseases, psychiatric conditions, or thyroid dysfunction were excluded. This was a prospective cross-sectional observational study. The NMSS was administered in person during routine outpatient visits by a trained neurologist. Demographic and clinical data, including medication use, gabapentin dosage, and comorbidities, were recorded contemporaneously using standardized forms and subsequently entered into the hospital database for analysis.

MAIN POINTS

- Patients receiving gabapentin reported significantly higher non-motor symptom scores compared with healthy controls, as assessed by the Non-Motor Symptom Scale (NMSS).
- Salivation, constipation, urinary urgency or nocturia, pain, memory impairment, depression, anxiety, sexual dysfunction, orthostatic hypotension, daytime sleepiness, leg edema, and sweating were significantly more frequent among gabapentin users.
- This study is the first to systematically assess non-motor symptoms in gabapentin users with the NMSS, highlighting a broad range of underrecognized complaints.
- The NMSS may serve as a structured tool for the systematic screening of non-motor symptoms in patients receiving gabapentin in routine clinical practice.
- Findings are exploratory, but suggest the need for prospective, indication-matched studies to confirm and clarify the associations between gabapentin and non-motor symptoms.

The Turkish-validated NMSS for Parkinson's disease was administered to gabapentin users and healthy controls. The control group consisted of age- and sex-matched healthy individuals who were not using gabapentin or any other medications affecting the central nervous system. All control participants were recruited from the same outpatient clinic to minimize selection bias. Potential confounding factors, such as diabetes mellitus, thyroid dysfunction, cardiovascular diseases, psychiatric disorders, or systemic inflammatory diseases, were explicitly excluded from both groups. Comorbidities were reviewed using detailed medical histories and current medication records to ensure comparability between groups. The NMSS consists of 30 yes/no items covering gastrointestinal, genitourinary, cardiovascular, attention/memory, perception, mood, and sleep domains. The items are scored as 1 (yes or presence) or 0 (no or absence).[8]

Patients with at least 120 days of gabapentin use were included because long-term adverse effects typically emerge after 3-4 months .[4,9]

Data were retrieved from Mengücek Gazi Training and Research Hospital's database. The study was approved by the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (approval no.: 14/11, dated: 10.01.2022). The study was conducted in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki (1964) and its later amendments.

Statistical Analysis

The sample size was determined based on a priori power analysis using G*Power version 3.1.9.7 (Heinrich Heine University Düsseldorf, Düsseldorf, Germany). The analysis indicated that a minimum sample size of 52 subjects was required. Additionally, a post-hoc power analysis indicated that the study had 99% power. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The distributions of continuous variables were assessed for normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Descriptive statistics were presented as mean ± standard deviation for continuous variables and as frequencies (n, %) for categorical variables. For comparisons of total NMSS scores between groups, the Independent samples t-test was applied. For categorical symptom data (yes/no responses), chi-square tests were used, with Fisher's exact test applied when expected cell counts were less than.[5] Correlation analyses were performed using Spearman's rho for non-normally distributed

variables. Spearman's rank correlation test was used to evaluate associations between daily gabapentin dose, age, and total NMSS scores within the gabapentin-treated group. A *P* value < 0.05 was considered statistically significant.

RESULTS

The study included 105 patients receiving gabapentin and 107 demographically matched healthy controls. The demographic characteristics of the groups are presented in Table 1. Statistical analysis revealed no significant differences between the groups in terms of sex or age ($P > 0.05$ for both). Indications for gabapentin use are listed in Table 2.

The NMSS was administered to patients receiving gabapentin treatment and to healthy controls. The total NMSS score was significantly higher in the gabapentin group than in the control group (11.6 ± 5.56 vs. 6.03 ± 4.28, $P < 0.001$). Item-based results are summarized in Table 3. Salivation, gastrointestinal, urinary, neuropsychiatric, and autonomic symptoms were significantly more frequent in the gabapentin group than in controls. Among gabapentin users, daily doses ranged from 200 to 1800 mg/day (median = 850 mg/day). No significant correlation was found between daily gabapentin dose and total NMSS score ($P = 0.21$). In contrast, age was positively correlated with the total NMSS score among gabapentin users ($P = 0.006$). No significant association between age and NMSS score was observed in the control group, likely due to minimal variability in non-motor symptom reporting.

DISCUSSION

In the present study, the total NMSS score was significantly higher in the gabapentin-user group than in the control group. To the best of our knowledge, this is the first study to evaluate NMS during gabapentin treatment using a structured screening tool. While many of the individual complaints observed in our cohort, such as constipation, salivation, and sexual dysfunction, have previously been reported as adverse effects of gabapentin, our study is novel in systematically assessing these symptoms with the NMSS in a relatively large sample of gabapentin-treated patients.

The novelty of our findings does not lie in identifying previously unrecognized side effects, but rather in providing a systematic overview of non-motor domains potentially affected by gabapentin. By applying the NMSS as a structured screening tool, we captured a wide range of symptoms often underreported in routine clinical practice, thereby providing a more comprehensive profile of gabapentin's tolerability. These results should be considered exploratory and hypothesis-generating, underscoring the need for future studies using validated adverse events or quality-of-life instruments to confirm and extend our observations.

Items 1, 3, 4, 5, 6, and 7 of the NMSS pertain to gastrointestinal dysfunction. In our cohort, excessive salivation and constipation were significantly more common among gabapentin-treated patients than among controls. Hypersalivation has a reported prevalence of 6%-15% in healthy individuals.[10], but no clinical studies have specifically investigated salivation during gabapentin treatment in humans. A feline study reported post-gabapentin hypersalivation, although it was unclear whether this was a pharmacological effect or related to stress or oral irritation from administration.[11]

There were no statistically significant differences between the groups regarding dysphagia or nausea/vomiting. Gabapentin has been shown to improve swallowing function after radiotherapy and head and neck surgery, likely by reducing neuropathic pain rather than through a direct effect on swallowing mechanics.[12] Although nausea and vomiting are recognized adverse effects of gabapentin[5], studies have also shown its effectiveness in the treatment of hyperemesis gravidarum. Conversely, one study reported no statistically significant effect of gabapentin on chemotherapy-related nausea and vomiting.[13,14] These divergent outcomes likely reflect differences in patient populations and treatment indications.

In the present study, the prevalence of constipation was significantly higher in the gabapentin-user group than in the control group. Constipation is a known side effect of gabapentin, generally of mild to moderate severity.[15] The mechanism remains unclear, but it may involve reduced neuronal excitability and decreased release of neurotransmitters such as glutamate and substance P. Paradoxically, gabapentin has been shown to alleviate symptoms in diarrhea-predominant irritable bowel syndrome by enhancing rectal compliance and reducing rectal sensitivity.[16]

No statistically significant differences were observed for fecal incontinence or tenesmus between the groups. A case series of four patients reported that gabapentin and pregabalin alleviated cancer-related tenesmus, although the evidence remains limited.[17] The differing results reported in the literature may reflect the use of gabapentin in diverse patient populations with varying indications.

Table 1. Comparison of Demographic Characteristics Between the Gabapentin and Control Groups

Characteristic	Gabapentin group (n=105)	Control group (n=107)	*P* value
Sex, n (%)			0.919
Female	67 (63.8%)	67 (62.6%)	
Male	38 (36.2%)	40 (37.4%)	
Age (years)			0.164
Mean ± SD	57.7 ± 11.8	55.7 ± 9.8	

SD, standard deviation.

Table 2. Indications for Gabapentin Use (n=105)

Indication	Number of patients	Percentage (%)
Lumbar disc herniation	25	23.8%
Polyneuropathy	19	18.1%
Restless leg syndrome	20	19.1%
Cervical disc herniation	18	17.1%
Trigeminal neuralgia	7	6.67%
Carpal tunnel syndrome	7	6.67%
Fibromyalgia	6	5.71%
Ulnar nerve lesion	3	2.86%

Urinary dysfunction is assessed by questions 8 and 9 of the NMSS. In the present study, urinary urgency and nocturia were significantly more frequent among gabapentin users. Case reports describe gabapentin-associated urinary incontinence, thought to result from inhibitory effects on bladder C-fiber afferents and reduced detrusor contractility.[18] In contrast, Chua et al.[19] demonstrated that gabapentin was effective in the treatment of overactive bladder. In the same study, gabapentin was more effective than solifenacin in treating nocturia, an effect attributed to hypothalamic inhibition of bladder activity. These discrepancies may reflect differential effects of gabapentin in individuals with and without underlying urinary symptoms.

Questions 2, 10, and 29 of the NMSS pertain to the sensory domain. No statistically significant difference in olfactory function was observed between the groups. Published studies on gabapentin's effect on olfaction are limited to cohorts with COVID-19: one study reported no change in olfaction, while another, with a very small sample size, reported subjective improvement.[20,21]

To the best of our knowledge, there are no studies addressing gabapentin's impact on gustatory function.

Despite gabapentin's well-established efficacy in pain management, reported pain complaints were significantly higher in the gabapentin group than in controls. We attribute this finding to the underlying indications for gabapentin, rather than to a nociceptive side effect.

Table 3. NMSS Findings Across Study Groups

Symptom	Gabapentin group (n=105)		Control group (n=107)		*P* value
	Yes	No	Yes	No	
1.Increased salivation	13 (12.4%)	92 (87.6%)	3 (2.8%)	104 (97.2%)	**0.009**
2.Loss of taste/smell	13 (12.4%)	92 (87.6%)	9 (8.4%)	98 (91.6%)	0.343
3.Difficulty swallowing	14 (13.3%)	91 (86.7%)	7 (6.5%)	100 (93.5%)	0.098
4.Nausea/vomiting	18 (17.1%)	87 (82.9%)	9 (8.4%)	98 (91.6%)	0.057
5.Constipation	41 (39%)	64 (61%)	25 (23.4%)	82 (76.6%)	**0.014**
6.Fecal incontinence	14 (13.3%)	91 (86.7%)	7 (6.5%)	100 (93.5%)	0.098
7.Tenesmus	48 (45.7%)	57 (54.3%)	48 (44.9%)	59 (55.1%)	0.901
8.Urgency	61 (58.1%)	44 (41.9%)	76 (71%)	31 (29%)	**0.049**
9.Nocturia	84 (80%)	21 (20%)	50 (46.7%)	57 (53.3%)	**< 0.001**
10.Pain	68 (64.8%)	37 (35.2%)	21 (19.6%)	86 (80.4%)	**< 0.001**
11Weight change	20 (19%)	85 (81%)	2 (1.9%)	105 (98.1%)	**< 0.001**
12.Memory impairment	57 (54.3%)	48 (45.7%)	36 (33.6%)	71 (66.4%)	**0.003**
13.Apathy	39 (37.1%)	66 (62.9%)	26 (24.3%)	81 (75.7%)	**0.043**
14.Hallucinations	21 (20%)	84 (80%)	2 (1.9%)	105 (98.1%)	**< 0.001**
15.Attention deficits	43 (41%)	62 (59%)	25 (23.4%)	82 (76.6%)	0.006
16.Depression	69 (65.7%)	36 (34.3%)	30 (28%)	77 (72%)	**< 0.001**
17.Anxiety	44 (41.9%)	61 (58.1%)	20 (18.7%)	87 (81.3%)	**< 0.001**
18.Reduced libido	58 (55.2%)	47 (44.8%)	33 (30.8%)	74 (69.2%)	**< 0.001**
19.Sexual dysfunction	57 (54.3%)	48 (45.7%)	24 (22.4%)	83 (77.6%)	**< 0.001**
20.Orthostatic hypotension	60 (57.1%)	45 (42.9%)	27 (25.2%)	80 (74.8%)	**< 0.001**
21.Falls	35 (33.3%)	70 (66.7%)	14 (13.1%)	93 (86.9%)	**< 0.001**
22.Daytime sleepiness	21 (20%)	84 (80%)	9 (8.4%)	98 (91.6%)	**0.016**
23.Difficulty initiating/maintaining sleep	50 (47.6%)	55 (52.4%)	45 (42.1%)	62 (57.9%)	0.415
24.Vivid dreams	33 (31.4%)	72 (68.6%)	18 (16.8%)	89 (83.2%)	**0.013**
25.REM sleep behavior disorder	28 (26.7%)	77 (73.3%)	14 (13.1%)	93 (86.9%)	**0.013**
26.Restless leg syndrome	63 (60%)	42 (40%)	26 (24.3%)	81 (75.7%)	**< 0.001**
27.Leg edema	48 (45.7%)	57 (54.3%)	9 (8.4%)	98 (91.6%)	**< 0.001**
28.Sweating	52 (49.5%)	53 (50.5%)	19 (17.8%)	88 (82.2%)	**< 0.001**
29.Diplopia	26 (24.8%)	79 (75.2%)	6 (5.6%)	101 (94.4%)	**< 0.001**
30.Delusions	22 (21%)	83 (79%)	4 (3.7%)	103 (96.3%)	**< 0.001**

REM, Rapid eye movement; NMSS, Non-Motor Symptom Scale.

Diplopia was also reported significantly more often by gabapentin users. One study noted an 8% incidence of diplopia with 2,400 mg/day gabapentin treatment.[22] The mechanism by which gabapentin causes diplopia is not known.

Items 12-17 and 30 of the NMSS capture neuropsychiatric and cognitive complaints. In our cohort, "yes" responses to these items were more frequent in the gabapentin group than in controls. Memory and attention disturbances were notably higher among gabapentin users. Forgetfulness has been reported in 20% of gabapentin users and may be related to reduced glutamate release or suppression of neuronal hyperactivity.[23]

Gabapentin's psychiatric effects are inconsistent across studies. While some trials found no psychotropic effects, others demonstrated anxiolytic effects; gabapentin has shown benefit as an adjunct in bipolar disorder.[24]

In several cases where gabapentin was initiated in patients already receiving psychotropic medications, hallucinations and agitation were reported. Additionally, a single case report described a patient without prior psychiatric history who developed hallucinations, suicidal ideation, and agitation after gabapentin administration. Gabapentin-associated psychiatric side effects may be linked to elevated extracellular glutamate or downregulation of serotonin receptors.[25] Variability in findings may reflect differences in psychiatric background across study populations.

Sexual dysfunction is assessed by questions 18 and 19 of the NMSS. Both low- and high-dose gabapentin have been implicated in sexual side effects, possibly due to its inhibitory effects on neurotransmission.[26,27] In the present study, decreased libido and erectile or sexual dysfunction occurred significantly more frequently among gabapentin users. Libido is governed by limbic system pathways, while erectile function is regulated by autonomic circuits. Decreased libido is more often linked to hormonal and psychiatric factors, whereas erectile dysfunction is more commonly associated with vascular and neurogenic causes. Dopamine supports both libido and erection.[28]

Questions 20 and 21 of the NMSS relate to cardiovascular autonomic function and falls. In our cohort, orthostatic hypotension and falls were significantly more common among gabapentin users than controls. Chen et al.[29] observed that microinjection of gabapentin into the nucleus tractus solitarii of hypertensive rats induced hypotension and bradycardia via the nitric oxide synthase pathway. Moreover, clinical studies have shown that gabapentin substantially increases the the risk of falls in older adults, independent of cognitive function.[30,31]

Weight loss is among the known side effects of gabapentin, although its mechanism remains unknown.[32] In the present study, complaints of weight loss were significantly more frequent in the gabapentin group than in controls.

Questions 22-26 of the NMSS assess sleep complaints. In our cohort, with the exception of items related to sleep initiation, scores for sleep-related NMS were significantly higher in the gabapentin group. Somnolence is a known adverse effect of gabapentin.[33] No studies have evaluated the association between gabapentin and REM sleep behavior disorder.

RLS complaints were significantly more common in the gabapentin group than in the control group. We attribute this finding not to a side effect of gabapentin but to its use in patients with RLS.

Leg edema is assessed by questions 27 of the NMSS. This complaint was significantly more frequent in the gabapentin group. Gabapentin-induced peripheral edema is thought to result from reduced vascular autoregulation and increased vascular permeability.[5,34]

Excessive sweating is assessed by questions 28 of the NMSS. In our cohort, this complaint was more frequently reported by gabapentin users. Although no studies have directly examined excessive sweating as a side effect, gabapentin has shown efficacy in treating menopausal and cancer-related sweating and hot flashes.[35,36] The discrepancy between our findings and previous reports may relate to the inclusion of hormonally unstable patients in those studies. Gabapentin's effect on sweating may involve modulation of hypothalamic calcium channels. Gabapentin binds to α2-δ subunits of voltage-gated calcium channels, modulating the release of several neurotransmitters. These pharmacological effects may contribute to the broad range of NMS observed in clinical use.[37]

Although many adverse effects of gabapentin have been described as dose-dependent[38], our findings did not demonstrate a significant association between daily dose and total NMSS score. Conversely, a positive correlation between age and non-motor symptom burden was observed among gabapentin users but not in the control group, suggesting that aging-related factors may play a more prominent role than dosage in the manifestation of non-motor adverse effects. These findings highlight the importance of considering patient age when evaluating non-motor side effects associated with gabapentin therapy.

These results should therefore be viewed as exploratory. While the NMSS is not a validated instrument in this population, its use enabled the detection of a broad range of complaints that are often underreported in daily clinical practice. Future studies with disease-specific adverse event or quality-of-life measures are required to confirm the clinical significance of these findings.

Study Limitations

There are several limitations to the present study. First, we applied the NMSS, originally developed and validated for Parkinson's disease. Although the scale has not been formally validated in non-Parkinson's populations, its multidimensional structure enabled us to systematically assess a broad spectrum of non-motor domains relevant to gabapentin therapy, including gastrointestinal, urinary, neuropsychiatric, and sleep-related symptoms. For this reason, we considered the NMSS an appropriate exploratory tool. Second, the NMSS does not encompass all possible NMS and functions only as a screening instrument rather than providing a detailed quantitative assessment. For instance, behavioral aspects such as medication misuse or dependence are not captured within the NMSS domains, despite emerging evidence suggesting that

gabapentinoids may have potential for dependence.[38] Third, as gabapentin dosage was neither tapered nor discontinued in this study, the reversibility of non-motor adverse effects could not be evaluated. Furthermore, serum iron and ferritin levels were not assessed; therefore, the potential contribution of iron deficiency to the higher frequency of RLS among gabapentin users could not be evaluated. Autonomic function tests were not performed; therefore, the possibility that some NMS (e.g., orthostatic hypotension, sweating abnormalities, constipation) may reflect autonomic involvement in patients with polyneuropathy cannot be excluded. Finally, the study's cross-sectional observational design precludes causal inference; the associations observed should be interpreted as correlational rather than causal. Prospective studies with indication-matched controls are warranted to confirm and further elucidate these associations.

CONCLUSION

In this study, patients receiving gabapentin reported a higher frequency of NMS, as assessed by the NMSS, compared with healthy controls. These findings suggest a potential association between gabapentin use and NMS. However, they should be interpreted with caution due to the exploratory use of the NMSS, the heterogeneity of clinical indications, and the cross-sectional design. Additionally, the NMSS may serve as a practical tool for the systematic screening of potential side effects in clinical settings. Prospective studies with indication-matched control groups and validated assessment tools are warranted to confirm and clarify these associations.

Ethics

Ethics Committee Approval: The study was approved by the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (approval no.: 14/11, dated: 10.01.2022).

Informed Consent: Written informed consent was obtained from all participating patients.

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Footnotes

Author Contributions

Concept Design – C.T., A.E.; Data Collection or Processing – C.T., A.E.; Analysis or Interpretation – C.T., A.E.; Literature Review – C.T., A.E.; Writing, Reviewing and Editing – C.T., A.E.

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