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Retrospective Analysis of Gabapentin for Alcohol Withdrawal in the Hospital Setting: The Mayo Clinic Experience

Ruth E. Bates, MD; Jonathan G. Leung, PharmD, RPh; Robert J. Morgan, III, MD; Karen M. Fischer, MPH; Kemuel L. Philbrick, MD; and Simon Kung, MD

Abstract

Objective: To evaluate the efficacy and safety of a fixed-dose gabapentin taper protocol for alcohol withdrawal in hospitalized patients.

Patients and Methods: We retrospectively identified patients admitted to the hospital from January 1, 2016, to April 30, 2018, for alcohol withdrawal syndrome. Based on the treatment that patients received, they were divided into the gabapentin, benzodiazepine, and combination treatment groups. The primary outcome was length of stay, defined as time from admission to either discharge or 36 hours with Clinical Institute Withdrawal Assessment (CIWA) score less than 10. Inverse probability of treatment weight was used to account for differences in baseline characteristics between groups.

Results: A total of 443 patients met criteria for inclusion (128, 253, and 62 patients in the gabapentin, benzodiazepine, and combination groups, respectively). Baseline characteristics were similar among all groups. The median gabapentin group length of stay was 4.0 hours shorter than the benzodiazepine group (P=.012). Maximum CIWA score was 2.2 points lower in the gabapentin group (P=.003). No statistical differences were noted among safety outcomes, including incidence of seizure, intensive care unit transfer, or delirium tremens. Results were not statistically altered by inverse probability of treatment weight analysis.

Conclusion: A fixed-dose gabapentin taper protocol appears to be an effective and safe alternative to CIWA-driven benzodiazepines in patients hospitalized with alcohol withdrawal syndrome, though further research is necessary to define the potential subpopulations that benefit most.

From the Division of Hospital Internal Medicine (R.E.B.) and Departments of Pharmacy (J.G.L.), Psychiatry and Psychology (R.J.M., K.L.P., S.K.), and Health Sciences Research (K.M.F.), Mayo Clinic, Rochester, MN.

Alcohol use disorder (AUD) is the third leading modifiable cause of death in the United States.[1] Mortality may be associated with liver failure or abrupt alcohol cessation leading to severe alcohol withdrawal syndrome (AWS), seizures, and delirium tremens. When patients with long-term alcohol exposure suddenly cease alcohol intake, clinical signs and symptoms of AWS result from a combination of reduced γ-aminobutyric acid (GABA)ergic activity and enhanced glutamatergic activity, particularly mediated by N-methyl-D-aspartate receptors.[2] For the inpatient management of AWS, benzodiazepines that positively allosterically modulate GABA activity are considered the initial treatment of choice.[3] Benzodiazepines are typically given in a symptom-triggered approach using a clinical assessment tool such as the Clinical Institute Withdrawal Assessment (CIWA) of Alcohol Scale. This approach has been shown to decrease the quantity and length of exposure to benzodiazepines while also minimizing the progression to severe AWS and other sequelae of alcohol cessation.[4,5]

Despite its popularity, multiple concerns have been raised regarding CIWA-triggered benzodiazepine use. The CIWA tool includes many subjective or intentionally producible symptoms (eg, nausea and tremor) that may lead to artificially inflated CIWA scores and administration of unneeded benzodiazepines. Reliance on patient-reported symptoms also prevents its use in patients with altered mental status or inability to participate in assessment. In addition, benzodiazepines have been

associated with adverse effects such as oversedation, particularly in elderly patients or those with liver dysfunction. Respiratory depression secondary to high-dose benzodiazepine therapy can lead to respiratory failure requiring intensive care unit (ICU) transfer for intubation with associated increased length of stay (LOS) and morbidity.[6] Last, the abrupt discontinuation of benzodiazepine treatment has been associated with rebound anxiety and insomnia, which may increase the risk for relapse.[7,8]

Gabapentin has been studied as an attractive alternative to benzodiazepines for the treatment of AUD.[9] Gabapentin does not directly interact with GABA-A or GABA-B receptors. The mechanism of action by which gabapentin mitigates AWS is likely related to increasing GABA concentrations through direct GABA synthesis and interaction with the α2δ subunit of voltage-dependent calcium channels.[3,10] Gabapentin has sedative and anxiolytic properties, as well as utility in the setting of chronic neuropathic pain.[11] Gabapentin can also improve alcohol withdrawal—associated insomnia, which itself is associated with higher relapse risk.[12] Concerns about the abuse potential of gabapentin have been raised,[13] but it remains preferable to benzodiazepines, which are not recommended long term in patients with AUD. Multiple outpatient studies have evaluated the use of gabapentin for AUD.[9] Most studies have demonstrated benefit compared with placebo (particularly in reducing heavy drinking days), although the use of extended-release gabapentin was not associated with such benefits.[14]

There are limited data available regarding the use of gabapentin for AWS, particularly in the inpatient setting. When gabapentin is added to CIWA-directed benzodiazepine therapy, some studies have shown reduced benzodiazepine use and reduced LOS,[6,15] whereas others have not.[16-18] Even fewer studies have analyzed gabapentin monotherapy for AWS.[19,20]

At Mayo Clinic, a gabapentin protocol for AWS has been available since 2015, including a fixed-dose gabapentin taper. A prior 14-month evaluation of early use was previously described.[21] This study expands on that work to review the Mayo Clinic experience with this gabapentin protocol for AWS during its integration into the Hospital Internal Medicine practice. We hypothesized that patients treated with fixed-dose gabapentin taper would experience shorter clinically significant alcohol withdrawal with equivalent safety compared with those treated with CIWA-triggered benzodiazepines.

METHODS

We conducted a retrospective cohort study of adult patients 18 years or older who were hospitalized between January 1, 2016, and April 30, 2018, for the primary indication of alcohol withdrawal. Patients were categorized into 1 of 3 groups based on modality of AWS treatment: benzodiazepine, gabapentin, and combination. The benzodiazepine group comprised patients who received a standard CIWA-triggered benzodiazepine protocol. A maximum of 1 dose of gabapentin (over and above continuation of low-dose home gabapentin ≤900 mg total daily) during their hospitalization was allowed. The gabapentin group was comprised of patients who received 2 or more doses of gabapentin (totaling ≥900 mg total daily dose for at least 1 day) during their hospitalization and did not receive benzodiazepines after the initiation of gabapentin treatment. Continuation of home-scheduled benzodiazepine treatment was allowed. Patients not meeting criteria for either the benzodiazepine group or the gabapentin group comprised the combination group. This group included patients started concurrently on fixed-dose gabapentin taper and CIWA-triggered benzodiazepines, which was common during the initial adoption of the gabapentin protocol into clinical practice. This group also included patients who received benzodiazepines before switching to gabapentin (or a combination of gabapentin and benzodiazepines) or patients who received more than 1 dose of gabapentin before switching to benzodiazepines.

Gabapentin dosing was determined by provider preference, but the gabapentin protocol available during the study period recommended gabapentin in a burst and taper fashion. For patients with estimated glomerular filtration rates greater than 60 mL/min, dosing was 900 mg 3 times daily for 4 days, 600 mg 3 times daily for 3 days, 300 mg 3

times daily for 2 days, and then discontinuation. For patients with estimated glomerular filtration rates of 30 to 60 mL/min, dosing was 600 mg 3 times daily for 4 days, 300 mg 3 times daily for 3 days, 100 mg 3 times daily for 2 days, and then discontinuation. Patients were discharged when medically stable from symptoms of alcohol withdrawal and were typically given a prescription for the remaining days of the gabapentin taper.

Optional adjuvant medications available under the protocol included: (1) divalproex sodium taper for patients with prior severe alcohol withdrawal or history of traumatic brain injury without severe hepatic dysfunction (750 mg twice daily for 1 day, 500 mg twice daily for 5 days, and 250 mg twice daily for 3 days), (2) clonidine for significant hypertension in the setting of alcohol withdrawal (0.1 mg 3 times daily as needed), and (3) thiothixene or haloperidol for severe agitation and hallucinations. Use of these adjuvant medications was at the discretion of medical providers.

Exclusion criteria included initial admission to the ICU, discharge within 24 hours, primary seizure disorder, known gabapentin allergy or intolerance, concurrent intoxication or overdose involving substances other than alcohol or cannabis, and preadmission gabapentin use greater than 900 mg daily. Patients initiated on treatment with adjuvant medications (such as antipsychotics or anticonvulsants) other than divalproex, clonidine, thiothixene, or haloperidol were also excluded. In patients with more than 1 qualifying hospitalization during the study period, the first qualifying hospitalization was defined as the index hospitalization.

Study outcomes compared the gabapentin and benzodiazepine groups. The combination group was included only descriptively due to the high heterogeneity of treatments received. The primary outcome was LOS, defined as hours from admission to either discharge or 36 hours with CIWA scores less than 10. In effect, this LOS reflected the duration of clinically significant alcohol withdrawal. The definition of this outcome was intended to eliminate confounding from prolonged hospitalizations due to comorbid non—AWS-associated conditions or disposition challenges including civil commitment for chemical

dependency. Secondary outcomes included the occurrence of alcohol withdrawal seizure, delirium tremens, ICU transfer, total benzodiazepines received in lorazepam equivalents, and CIWA scores. Demographic variables, number of admissions for alcohol detoxification in the previous 12 months, history of alcohol withdrawal seizures and delirium tremens, previous gabapentin use for alcohol withdrawal, and the Charlson medical comorbidity index scores were collected or calculated for comparisons among the groups.

For continuous and categorical variables, t tests and χ^2 test were used, respectively, to compare characteristics of the gabapentin and benzodiazepine groups. For the primary and secondary outcomes, Mann-Whitney tests were used to determine differences between groups with continuous outcomes. Categorical outcomes were analyzed using Fisher exact test.

Due to the possibility that other covariates would influence which treatment a patient received and the LOS, the inverse probability of treatment weight (IPTW) was used. The propensity score for being treated with gabapentin was estimated using a logistic regression model incorporating the following pretreatment variables: age, sex, number of prior admissions with alcohol withdrawal, prior documented alcohol withdrawal seizures or delirium tremens, prior treatment of alcohol withdrawal with gabapentin, prior alcohol withdrawal seizure (or delirium tremens or ICU transfer) while being treated with gabapentin for alcohol withdrawal, reported or suspected alcohol withdrawal seizure within 48 hours of admission, admission CIWA score, admission date, and Charleston Comorbidity Index score (calculated using admission data and 30 days before admission). Standardized differences were analyzed to ensure that the covariates were balanced between groups. The propensity weighting was used in linear regression models for the continuous outcome variables, and logistic regression models, for the categorical variables. The LOS and area under the curve for CIWA scores greater than 10 did not meet the requirement of normal residuals and were log-transformed. The model with the outcome for maximum CIWA score was adjusted for CIWA score on admittance. $P<.05$ was considered statistically

significant in all models. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc).

RESULTS

During the study period, 443 patients met inclusion criteria. Baseline characteristics are presented in Table 1. There were no statistically significant differences with regard to mean Charlson Comorbidity Index score, admission CIWA score, number of prior admissions for alcohol withdrawal within the last 12 months, history of alcohol withdrawal seizures and delirium tremens, and previous treatment with gabapentin for alcohol withdrawal between the gabapentin (n=128) and benzodiazepine (n=253) groups. In the combination group (n = 62), most patients (45; 72.6%) were started on both treatments on admission. Of the 3 patients in the combination group started initially on the gabapentin protocol, 1 patient later received benzodiazepines due to clinical deterioration with high CIWA scores and 2 patients received benzodiazepines for anxiety. Of the 14 patients in the combination group started initially on benzodiazepine treatment, 2 patients were transitioned to the gabapentin protocol out of clinical concern for high benzodiazepine requirements, 6 were transitioned based on recommendations from Psychiatry, and 6 patients were transitioned in preparation for discharge.

Table 2 summarizes medications provided during the LOS (admission to either discharge or 36 hours of CIWA scores <10). Patients in the gabapentin, benzodiazepine, and combination groups were treated with lorazepam-equivalent median doses of 2, 5, and 9 mg, respectively. Most patients (n=374; 84.4%) received no adjuvant medications.

Study outcomes are shown in Table 3. The gabapentin group median LOS was 4 hours shorter than the benzodiazepine group (38 vs 42 hours; P=.012). All 5 seizures and 3 ICU transfers documented during the study period occurred in the benzodiazepine group, but there were no statistically significant differences between groups for either seizure (P=.173) or delirium tremens (P=.494). The mean maximum CIWA score (excluding admission CIWA score) in the gabapentin group was 2.2 points lower than in the benzodiazepine group (10.1 vs 12.3; P=.003).

TABLE 1. Baseline Characteristics[a]				
	Gabapentin (N=128)	Lorazepam (N=253)	Both (N=62)	P[b]
Age (y)				.506
Mean ± SD	49.8±12.6	48.9±13.2	43.0±10.0	
Min, max	22, 87	20, 90	21, 63	
Sex, no. (%)				.144
Female	42 (32.8)	65 (25.7)	19 (30.7)	
Male	86 (67.2)	188 (74.3)	43 (69.4)	
Race, no. (%)				.057
White	119 (93.0)	225 (88.9)	54 (87.1)	
Other	5 (3.9)	25 (9.9)	5 (8.1)	
Unknown	4 (3.1)	3 (1.2)	3 (4.8)	
Charlson Comorbidity Index score				.929
Mean ± SD	1.1±1.6	1.1±1.8	0.9±1.3	
Min, max	0, 7	0, 9	0, 5	
Admission CIWA score[c]				.922
Mean ± SD	8.1±5.7	8.0±6.0	9.5±6.1	
Min, max	0, 28	0, 33	2, 28	
No. of prior admits for alcohol withdrawal in last 12 mo				.767
Mean ± SD	0.3±1.3	0.4±1.0	0.3±0.8	
Min, max	0, 11	0, 8	0, 5	
History of alcohol withdrawal seizures and delirium tremens, no. (%)				.819
Yes	37 (28.9)	76 (30.0)	22 (35.5)	
No	91 (71.1)	177 (70.0)	40 (64.5)	
Prior treatment with gabapentin for alcohol withdrawal, no. (%)				.759
Yes	7 (5.5)	12 (4.7)	8 (12.9)	
No	121 (94.5)	241 (95.3)	54 (87.1)	
Prior poor outcome when treated with gabapentin for alcohol withdrawal, no. (%)				.313
Yes	0 (0)	2 (0.8)	1 (1.6)	
No	128 (100)	251 (99.2)	61 (98.4)	

[a]CIWA = Clinical Institute Withdrawal Assessment ; max = maximum; min = minimum.
[b]The t test for continuous variables and χ^2 test or Fisher exact test for categorical variables for gabapentin vs lorazepam.
[c]Missing data: 1 missing from gabapentin group, 1 missing from lorazepam group.

Among patients with an LOS greater than 36 hours (n=336), the AUC for CIWA scores of 10 or higher was not statistically different between groups (P=.142). All outcome results

TABLE 2. Medications Received During Length of Stay[a]			
	Gabapentin (n=128)	Lorazepam (n=253)	Combination (n=62)
Total gabapentin (mg)			
Median (Q1, Q3)	3600 (3300, 5400)	0 (0, 0)	3600 (2250, 5400)
Min, max	600, 9200	0, 5400	600, 17,700
Total benzodiazepines (mg)			
Median (Q1, Q3)	2 (0, 4)	5 (1, 15)	9 (4.5, 19)
Min, max	0, 144.5[b]	0, 197	0,[c] 282
Sodium valproate (mg)			
Median (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Min, max	0, 4250	0, 5000	0, 5000
Clonidine (mg)			
Median (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Min, max	0, 0.6	0, 1.1	0, 0.4
Haloperidol (mg)			
Median (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Min, max	0, 12.5	0, 17	0, 5
Thiothixene (mg)			
Median (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Min, max	0, 10	0, 4	0, 0

[a]CIWA = Clinical Institute Withdrawal Assessment; Max = maximum; Min = minimum; Q = quartile.

[b]One patient with prolonged alcohol withdrawal was switched from CIWA-directed benzodiazepine to gabapentin therapy due to high benzodiazepine use. He met criteria for the gabapentin protocol group because he did not receive benzodiazepines after the initiation of gabapentin therapy.

[c]One participant in the combined group received no CIWA-directed benzodiazepines but failed to meet criteria for either the gabapentin protocol group or the benzodiazepine group due to low-dose gabapentin (300 mg 3 times daily) started on admission.

were not significantly altered by IPTW (see Supplemental Appendix, available online at https://mcpiqojournal.org).

DISCUSSION

This retrospective cohort study suggests that a fixed-dose gabapentin protocol for alcohol withdrawal can be an effective alternative to CIWA-driven benzodiazepine therapy for patients hospitalized with AWS. To our knowledge, this is the largest study of its kind, including 443 hospitalized patients over a nearly 2.5-year period. We also sought to avoid confounding of the primary outcome by defining LOS to reflect clinically active withdrawal rather than simply hours of hospitalization. Our study is also one of the few to directly compare gabapentin monotherapy vs benzodiazepines. The primary outcome demonstrates a slightly shorter LOS for patients treated for AWS with gabapentin compared with benzodiazepines, with no difference in

adverse outcomes including seizures, delirium tremens, or ICU transfers. Maximum CIWA scores were 2.2 points lower in the gabapentin group, although the clinical significance of this finding is unclear.

A review of gabapentin for AWS in 77 inpatients for an earlier period at Mayo Clinic showed the same apparent efficacy and safety but did not show a statistically significant difference in LOS.[21] However, this current study defined LOS from admission to either discharge or 36 hours of CIWA scores lower than 10, either of which suggested completion of clinically significant alcohol withdrawal. This definition of LOS was designed to account for patients whose prolonged hospitalizations were secondary to non–AWS-related conditions.

Multiple studies have evaluated the use of gabapentin for AWS in hospitalized patients since the publication of our preliminary analysis. Those using gabapentin as an adjunct medication in addition to CIWA-directed benzodiazepines have shown mixed results. A retrospective review of 50 patients who received at least 1800 mg per day of gabapentin in the first 48 hours of AWS compared with 50 propensity-matched patients who received benzodiazepines found that the gabapentin group required lower benzodiazepine doses and had a shorter LOS.[15] In contrast, 3 other retrospective studies[16-18] used gabapentin to augment AWS management and found no reduction in benzodiazepine use. However, patients in Vadiei et al[18] and Nichols et al[17] received lower mean doses of gabapentin per day compared with Levine et al[15] (1000 and 1200 mg per day, respectively). Those studied by Anduluz et al[16] received a total of 2100 mg of gabapentin on day 1 and 1800 mg on day 2. However, in their study, the patients treated with gabapentin were older and exhibited more severe alcohol withdrawal symptoms than the control group.

Rather than use gabapentin as an adjunct to benzodiazepine therapy, our study primarily sought to contrast gabapentin and benzodiazepine monotherapies while still describing outcomes in the heterogeneous combination group. A somewhat similar study reviewed 50 patients pre- and 50 patients postimplementation of an institutional guideline and order set using a high-dose gabapentin taper

(starting with 2800 mg on day 1 for those younger than 65 years and 2000 mg on day 1 for those older than 65 years).[22] They found lower benzodiazepine use and a shorter LOS following the implementation, though scheduled and as-needed benzodiazepines remained available based on CIWA scores and provider preference.

Our results are also similar to the 2 prior randomized studies that assessed gabapentin monotherapy for AWS. Anton et al[19] conducted a 16-week randomized controlled trial using gabapentin (titrated over 5 days to a maximum dose of 1200 mg per day) vs placebo for the treatment of AUD in patients with alcohol withdrawal symptoms. They demonstrated improved total abstinence and reduced heavy drinking days, particularly among patients with high alcohol withdrawal symptoms. Similarly, Myrick et al[20] conducted an outpatient double-blinded trial in which patients with AWS were randomly assigned to treatment with gabapentin (900 mg tapering to 600 mg vs 1200 mg tapering to 800 mg) vs lorazepam for 4 days. Those treated with gabapentin (particularly the higher dose group) demonstrated lower CIWA scores and less relapse during the 12-day follow-up period.[20]

Available evidence suggests that gabapentin is associated with low rates of adverse effects and often improves withdrawal symptoms, including cravings, anxiety, and insomnia. However, our data did not allow us to conclusively determine whether use of gabapentin for AWS is safe in all patients or should be reserved for those with mild to moderate AWS. In our study, 3 patients with poor prior outcomes while being treated with gabapentin for AWS were preferentially treated with benzodiazepines or combination therapy. Additionally, more patients met criteria for the benzodiazepine group (n=253) than the gabapentin group (n=128), perhaps suggesting provider preference for benzodiazepines for anticipated severe AWS or lack of familiarity with gabapentin. Nevertheless, although 1 patient in the combination group was switched from gabapentin to benzodiazepine treatment out of concern for clinical deterioration, many more patients (n=14) were switched from benzodiazepines to gabapentin due to clinical

TABLE 3. Outcomes[a]			
	Gabapentin (n=128)	Lorazepam (n=253)	P[b]
Transferred to ICU for any reason, no. (%)			.554[c]
Yes	0 (0)	3 (1.2)	
No	128 (100)	250 (98.8)	
Seizure during hospitalization, no. (%)			.173[c]
Yes	0 (0)	5 (2.0)	
No	128 (100)	248 (98.0)	
Delirium tremens documented during this hospitalization, no. (%)			.494[c]
Yes	9 (7.0)	23 (9.1)	
No	119 (93.0)	230 (90.9)	
Length of stay (h)[d]			.012
Mean ± SD	44.8±15.8	54.7±29.1	
Median (Q1, Q3)	38 (36, 49)	42 (36, 66.5)	
Min, max	24, 118	24, 188	
Area under the curve[d]			.142
Mean ± SD	13.0±25.5	19.5±36.9	
Median (Q1, Q3)	0 (0, 15.3)	0.5 (0, 22.0)	
Min, max	0, 127.3	0, 253.9	
Max CIWA score[d]			.003
Mean ± SD	10.1±5.2	12.3±6.8	
Median (Q1, Q3)	9 (7, 13)	11.5 (7, 17)	
Min, max	0, 31	0, 33	

[a]CIWA = Clinical Institute Withdrawal Assessment; ICU = intensive care unit; Max, maximum; Min = minimum; Q = quartile.
[b]Mann-Whitney test between the gabapentin and lorazepam groups.
[c]Fisher exact test between the gabapentin and lorazepam groups.
[d]Missing data: 1 missing from the gabapentin group, 1 missing from the lorazepam group.

deterioration, Psychiatry recommendation, or to reduce cravings and promote abstinence following discharge. Furthermore, baseline characteristics of the gabapentin and benzodiazepine groups were not statistically different (Table 1) in terms of AWS severity. These findings suggest there may be a mismatch between providers' perception of gabapentin's safety for treating AWS and its actual safety profile. Further research is needed to elucidate this potential discrepancy.

There are several limitations to our study. First, it is retrospective in nature. Although baseline characteristics were not statistically different and IPTW analysis did not affect the results of the study, we cannot rule out the possibility of confounding factors influencing which patients were selected for gabapentin therapy. Treatment decisions may have been biased by perception of the

efficacy of gabapentin or concerns raised by features of the patient's alcohol withdrawal history that were uncaptured by our data.

Second, our study was not statistically powered to detect small differences in adverse events such as seizure and delirium tremens though our findings are consistent with the existing literature suggesting that gabapentin is typically well tolerated and does not worsen outcomes.

Third, our study is an analysis of a single tertiary referral hospital and our findings may not be generalizable to other populations or settings. Fourth, we were not able to analyze postdischarge data to evaluate rates of relapse or readmission.

CONCLUSION

Our study suggests that gabapentin monotherapy is effective for the treatment of patients hospitalized with AWS, with some evidence of superiority over CIWA-directed benzodiazepine therapy. Future research, particularly prospective randomized controlled trials, is needed to confirm these findings and determine potential subgroups of patients who could benefit most from gabapentin therapy.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at https://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Correspondence: Address to Ruth E. Bates, MD, Division of Hospital Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (bates.ruth@mayo.edu).

ORCID
Ruth E. Bates: https://orcid.org/0000-0002-2035-9614; Jonathan G. Leung: https://orcid.org/0000-0003-3836-9375; Robert J. Morgan: https://orcid.org/0000-0003-0103-2090

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