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Real-World Phenobarbital Use, Treatment Escalation, and Clinical Outcomes in Critically Ill Patients With Alcohol Withdrawal Syndrome: A Multicenter Propensity-Matched Cohort Study

IMPORTANCE: Phenobarbital use in ICU alcohol withdrawal syndrome (AWS) may reflect severe or refractory withdrawal and treatment escalation, making multicenter data important to understand its use within ICU practice and its relationship with clinical outcomes.

OBJECTIVES: To evaluate phenobarbital use in real-world ICU AWS as a marker of severe or refractory withdrawal and treatment escalation. We also examined its association with time-to-discharge and safety outcomes compared with nonphenobarbital regimens.

DESIGN, SETTING, AND PARTICIPANTS: Multicenter retrospective cohort study using multiple imputation and propensity score matching. Adults with AWS, defined as Clinical Institute Withdrawal Assessment for Alcohol, revised (CIWA-Ar) score greater than or equal to 10, were included if they received a phenobarbital-based or nonphenobarbital-based regimen in ICUs across a large academic health system from June 30, 2017, to July 1, 2024. Postoperative ICU admissions were excluded.

MAIN OUTCOMES AND MEASURES: Primary outcomes were time to ICU and hospital discharge alive from treatment initiation. Safety outcomes were hypotension, new intubation, and aspiration within 48 hours.

RESULTS: Of 1216 patients, 345 (28.4%) received phenobarbital. Before matching, phenobarbital-treated patients had higher CIWA-Ar, Acute Physiology and Chronic Health Evaluation III, and pre-ICU benzodiazepine exposure, consistent with more severe or refractory withdrawal. In adjusted time-to-discharge models, phenobarbital use was not significantly associated with time to hospital discharge alive (discharge rate ratio [DRR], 0.91; 95% CI, 0.74–1.12; $p = 0.370$) or ICU discharge alive (DRR, 0.77; 95% CI, 0.59–1.01; $p = 0.057$). Hypotension and intubation were similar, and aspiration was less frequent with phenobarbital.

CONCLUSIONS: In a contemporary ICU cohort, phenobarbital use reflected treatment escalation in patients with more severe or refractory AWS. After adjustment, time to ICU and hospital discharge alive did not differ significantly, hypotension and intubation were similar, and aspiration was less frequent with phenobarbital. Future studies should define optimal timing, dosing, and patient selection.

KEYWORDS: alcohol withdrawal syndrome; intensive care unit; phenobarbital; propensity score matching; time to discharge alive

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KEY POINTS

Question: In critically ill adults with alcohol withdrawal syndrome (AWS), is real-world phenobarbital use a marker of severe or refractory withdrawal and treatment escalation, and how is it associated with clinical outcomes?

Findings: In this multicenter retrospective cohort of 1216 ICU patients, phenobarbital use was associated with more severe withdrawal and greater benzodiazepine exposure. In adjusted time-to-discharge models, phenobarbital was not significantly associated with time to hospital or ICU discharge alive. Hypotension and intubation were similar, and aspiration was less frequent with phenobarbital.

Meaning: In a contemporary ICU AWS practice, phenobarbital is used as treatment escalation in more severe or refractory withdrawal rather than a uniform treatment strategy. Clinical outcomes were largely similar. Prospective studies are needed to define optimal timing, dosing, and patient selection.

Alcohol withdrawal syndrome (AWS) is a frequent and high-risk complication in critical care, affecting up to 15% of ICU patients with alcohol use disorder (1). Severe AWS cases may require high-dose sedation and mechanical ventilation, prolonging ICU and hospital stay (2, 3). In a multicenter study, AWS was associated with a median increase in ICU length of stay (LOS) of 9 days and higher mortality when complicated by intubation (4).

Traditionally, benzodiazepines have been the cornerstone of AWS treatment, given their mechanism of action on the gamma-aminobutyric acid (GABA) type A receptor, which mediates the primary GABA effects of ethanol (5, 6). However, some patients do not respond adequately to benzodiazepines, a condition known as benzodiazepine-refractory AWS (7). In these instances, there is a critical need for adjunctive therapy, although robust evidence to guide these decisions remains limited.

Phenobarbital is a long-acting barbiturate that may offer several theoretical and practical advantages in this setting. It enhances GABAergic inhibition while also suppressing excitatory neurotransmission through modulation of glutamate receptors (8). This

dual mechanism of action, combined with a predictable pharmacokinetic profile and long half-life, makes phenobarbital an appealing option for both monotherapy and adjunctive therapy in severe or benzodiazepine-refractory AWS. Several studies have suggested that phenobarbital-based strategies may reduce ICU and hospital LOS, decrease the rate of intubation (3, 9, 10), and allow for earlier symptom control compared with traditional Benzodiazepine-based regimens (11). However, other investigations have reported neutral or conflicting results, and practice patterns remain highly variable across institutions (12, 13).

Despite its increasing usage, there remains a lack of multicenter real-world data describing how phenobarbital is used in critically ill patients with AWS and how its use relates to treatment escalation, time to discharge, and safety outcomes. Existing literature is often limited to single-center designs, small sample sizes, and variable adjustment for confounding (9, 10, 12, 13). To address these knowledge gaps, we conducted a multicenter, retrospective cohort study comparing phenobarbital to nonphenobarbital-based pharmacologic regimens in ICU patients with AWS. Using a propensity score-matching framework, our objective was to evaluate phenobarbital use in real-world ICU AWS as a marker of severe or refractory withdrawal and treatment escalation, and to examine its association with time to ICU and hospital discharge and early safety outcomes.

METHODS

The Mayo Clinic Institutional Review Board reviewed this study and determined it to be exempt (Protocol 24-003052; April 4, 2024). The requirement for informed consent was waived. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies (**Fig. 1; eTable 1**, <https://links.lww.com/CCX/B672>).

Design, Setting, and Participants

This retrospective, multicenter cohort study evaluated critically ill adults admitted with AWS to ICUs across large academic medical centers in Arizona, Florida, Minnesota, and multiple Midwest sites in both Minnesota and Wisconsin between June 30, 2017, and July 1, 2024. Eligible patients were 18 years or older, had a diagnosis of AWS with a Clinical Institute Withdrawal

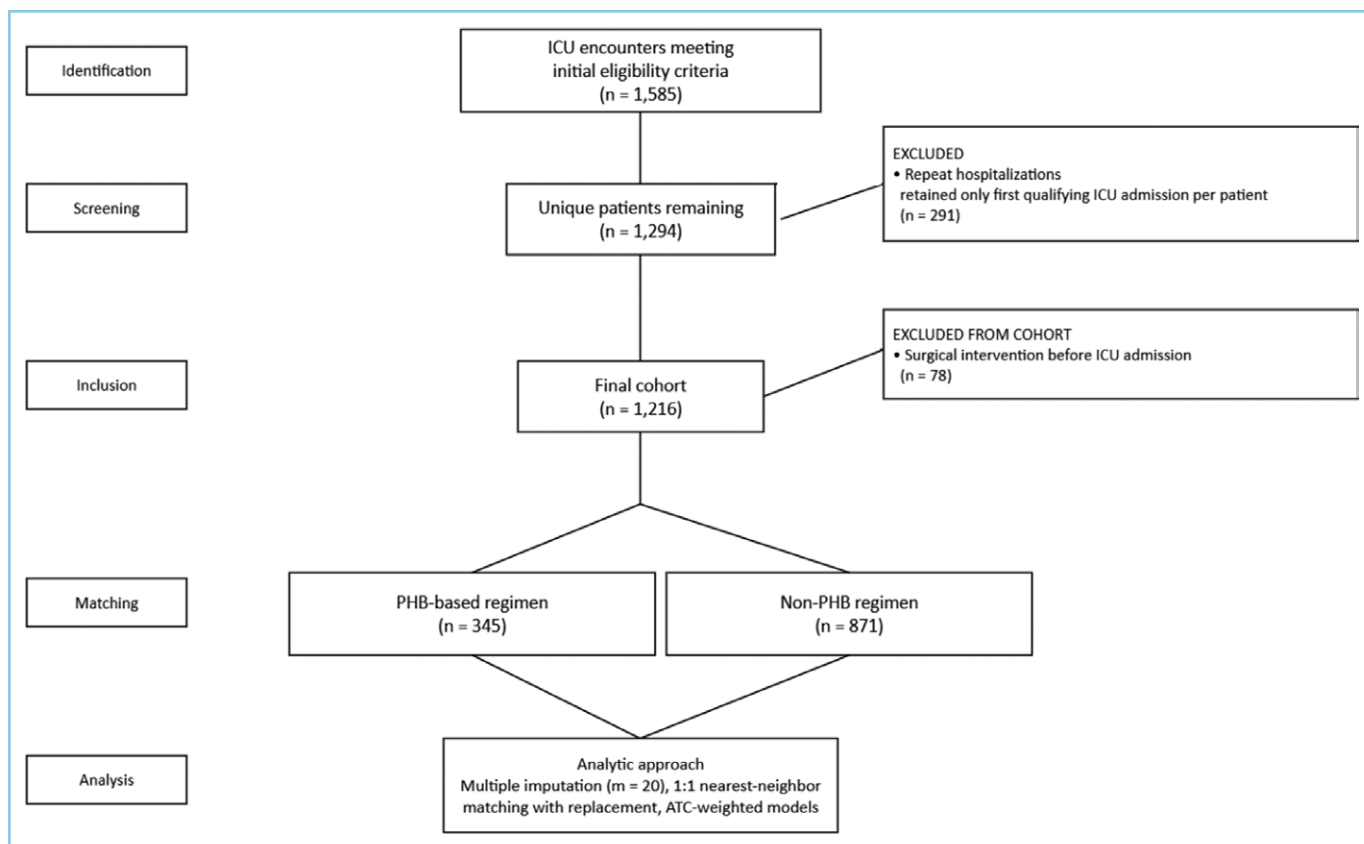


Figure 1. Study flow diagram. Flow diagram showing cohort assembly for the multicenter retrospective study of ICU patients with alcohol withdrawal syndrome, including exclusions for repeat hospitalizations and surgical intervention before ICU admission, final treatment groups (phenobarbital [PHB]-based vs. non-PHB regimen), and the analytic approach of multiple imputation, 1:1 nearest-neighbor propensity score matching with replacement, and average treatment effect in the control (ATC)-weighted models.

Assessment for Alcohol, revised (CIWA-Ar) score of 10 or greater, and received either a phenobarbital-based or nonphenobarbital regimen. Phenobarbital dosing was not standardized across sites and reflected local practice. Patients were excluded if they lacked Minnesota research authorization (required by state law for patients treated in Minnesota) or required a surgical intervention before ICU admission.

A predefined subgroup analysis was performed in patients treated at Midwest sites, as these sites represented the largest and most comparable subgroup in the cohort. This allowed us to assess whether the main findings were consistent in a more uniform practice setting.

Variable Definitions and Data Sources

Baseline demographics and clinical characteristics included age, sex, weight, home medications (benzodiazepines, opioids, phenobarbital), and a range of clinical comorbidities (e.g., depression, schizophrenia, bipolar

disorder, psychotic disorders, hypertension, cerebrovascular disease, chronic obstructive pulmonary disease [COPD], chronic kidney disease, diabetes, and alcoholic liver disease). Psychiatric and medical comorbidities were identified using the *International Classification of Diseases*, 10th Revision (ICD-10) diagnostic codes and documented past medical history in the electronic health record (EHR). History of Alcohol-related seizures and delirium tremens (DTs) were also captured via EHR and ICD-10 codes (G40.5 for alcohol-related seizures and F10.231 for DT).

Clinical severity markers included the Charlson Comorbidity Index and CIWA-Ar scores, which were recorded at both the time of ICU admission and at treatment initiation (T0) to assess AWS severity. Pre-ICU Benzodiazepine exposure was captured as cumulative lorazepam equivalents administered before ICU admission. Laboratory markers at baseline included aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and serum ethanol levels, measured closest to ICU admission.

The intervention of interest was the use of a phenobarbital-based regimen for AWS management. This included any phenobarbital use after ICU admission, whether as monotherapy or with other sedatives. The comparator group consisted of patients treated without phenobarbital. Nonphenobarbital regimens could include benzodiazepines, propofol, dexmedetomidine, ketamine, clonidine, gabapentin, and antipsychotics alone or in combination.

Time zero (T0) was defined as the first pharmacologic treatment for AWS after ICU admission. Patients were classified as phenobarbital based if they received phenobarbital at any time after T0 during the ICU stay; others were classified as nonphenobarbital. Since phenobarbital could be started later as escalation therapy, time-to-discharge analyses began at treatment initiation, defined as first phenobarbital administration in the phenobarbital group and first benzodiazepine administration in the nonphenobarbital group. Benzodiazepine and phenobarbital exposure were summarized cumulatively through 48 hours, ICU discharge, and hospital discharge.

Outcomes

Primary outcomes were time from treatment initiation to ICU discharge alive and time from treatment initiation to hospital discharge alive. These outcomes were modeled as time-to-discharge outcomes, with discharge alive as the event. Safety outcomes included hypotension, defined as any mean arterial pressure (MAP) less than 65 mm Hg within 48 hours of treatment initiation, and respiratory compromise, defined as new intubation or aspiration within 48 hours of treatment initiation. New intubation was defined as initiation of invasive mechanical ventilation after treatment initiation among patients not mechanically ventilated at treatment initiation. Patients who were already mechanically ventilated at treatment initiation, including those intubated before ICU admission, were included in the overall cohort but were not considered at risk for the new-intubation outcome. Aspiration was identified within 48 hours of treatment initiation using ICD-10 code J69.0 and EHR search for documented aspiration events. CIWA-Ar change from treatment initiation to 24–48 hours was evaluated among patients with available scores and was considered exploratory because ICU CIWA-Ar documentation was incomplete.

Statistical Analysis

The multiple imputation by chained equations (MICE) algorithm was used to create 20 complete datasets. All outcome variables and potential confounders were used in the imputation models. Predictive mean matching and logistic regression were used to impute the numeric and categorical variables in the MICE technique, respectively. We assumed the data were missing at random, such that missingness could be explained by observed variables included in the imputation model.

Covariates for the propensity score model were selected a priori using clinical knowledge and a conceptual framework identifying baseline factors expected to influence both phenobarbital use and clinical outcomes. These included demographics, home medications, psychiatric and medical comorbidities, alcohol withdrawal history, baseline laboratory values, withdrawal severity, acute illness severity, and pre-ICU benzodiazepine exposure. Post-treatment benzodiazepine exposure and adjunctive sedative therapies were not included in the baseline propensity model because these variables may reflect downstream treatment escalation rather than baseline confounding.

In each of the 20 complete datasets, propensity scores for phenobarbital group assignment were estimated using logistic regression with main effects for age, gender, weight, home medications (benzodiazepines, opioids, and phenobarbital), past medical history (depression, schizophrenia, bipolar disorder, psychotic disorder, hypertension, cerebrovascular disease, COPD, chronic kidney disease, diabetes, alcoholic liver disease, seizures, DTs), Charlson comorbidity index, baseline laboratories (ethanol, AST, ALT, and total bilirubin), baseline CIWA, CIWA at treatment initiation, Acute Physiology and Chronic Health Evaluation (APACHE) III score, and cumulative lorazepam before ICU admission. Within each dataset, 1:1 nearest neighbor matching with replacement was performed using 0.2 times the SD of the propensity score logit as a caliper. Matching with replacement was used to improve covariate balance and preserve the target population for the average treatment effect in the control (ATE) framework. The mean matched sample sizes across imputations were 236.5 patients in the phenobarbital group and 869.5 patients in the nonphenobarbital group; the corresponding median matched sample sizes were 237 and 869, respectively.

Corresponding matching weights were computed under an ATC framework, representing the treatment contrast among patients who otherwise would have been managed without phenobarbital. Across the imputed datasets, covariate balance was assessed, before and after matching, using standardized mean differences and proportion differences for the confounders. Covariate balance was found to be adequate. Other propensity score estimation methods were investigated (including lasso regression, ridge regression, generalized additive models, recursive partitioning, random forests, and the Covariate Balancing Propensity Score algorithm), in addition to modifications of the matching propensity score caliper. No other technique resulted in a substantial improvement in the covariate balance after matching.

Poisson regression models and logistic regression models were used to estimate the ATC within each of the 20 complete datasets using the matching weights as sampling weights. Time-to-discharge outcomes were analyzed using Poisson regression models with discharge alive as the event. Follow-up began at treatment initiation, defined as first phenobarbital administration in the phenobarbital group and first benzodiazepine administration in the nonphenobarbital group. Patients who died before discharge were censored at death, and ICU and hospital mortality were reported separately. Time-to-discharge estimates are reported as discharge rate ratios (DRRs), where a value less than 1 indicates a lower rate of discharge alive and therefore longer time to discharge. Safety outcomes were analyzed using logistic regression models. Final estimates were pooled across the 20 complete datasets using Rubin's rules. R software v. 4.2 was used for the analysis (R Core Team [2022]; R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>) using the tidyverse, arsenal, mice, MatchThem, cobalt, and survey R packages.

RESULTS

Among 1585 eligible ICU encounters, 1216 unique patients met final inclusion criteria after excluding repeat hospitalizations and surgical admissions; 345 received a phenobarbital-based regimen and 871 did not (Fig. 1). Baseline characteristics before treatment initiation (T0) of the two groups are reported in **Table 1**. Patients in the phenobarbital group were younger (47.4 vs. 50.6 yr) and more often male (82.0% vs. 67.9%).

They also had features consistent with more severe or refractory withdrawal, including higher rates of seizure disorder (33.9% vs. 25.8%) and DTs (47.5% vs. 29.7%), higher CIWA-Ar scores both at admission (17.4 vs. 16.0) and T0 (15.4 vs. 13.2), higher overall severity of illness as reflected by APACHE III (66.3 vs. 62.8), and greater pre-ICU benzodiazepine exposure (14.2 vs. 4.9 mg). Among phenobarbital-treated patients, the median time from ICU admission to first phenobarbital administration was 1.8 hours (0.3–12.3 hr).

Following multiple imputations and propensity score matching, covariate balance improved substantially with all standardized differences within ± 0.1 (**Fig. 2**). There were 50 in-hospital deaths, including eight of 345 patients in the phenobarbital group and 42 of 871 patients in the nonphenobarbital group. In-hospital mortality was 2.3% and 4.8%, respectively. Of the 29 ICU deaths, five occurred in the phenobarbital group and 24 occurred in the nonphenobarbital group, corresponding to ICU mortality of 1.4% and 2.8%, respectively. In unadjusted time-to-discharge models, phenobarbital was associated with a lower rate of ICU discharge after treatment initiation, while time to hospital discharge, hypotension, and intubation did not differ significantly (**eTable 2**, <https://links.lww.com/CCX/B672>). In adjusted ATC time-to-discharge models, phenobarbital was not associated with a statistically significant difference in time to hospital discharge alive (DRR, 0.91; 95% CI, 0.74–1.12; $p = 0.370$) or time to ICU discharge alive (DRR, 0.77; 95% CI, 0.59–1.01; $p = 0.057$). Adjusted odds of MAP less than 65 mm Hg and new intubation were similar between groups (**Table 2**). Rates of aspiration within 24 and 48 hours were significantly lower in the phenobarbital group (7.5% and 7.8%) compared with the nonphenobarbital group (12.3% and 12.6%; **Table 3**). CIWA-Ar improvement at 24 and 48 hours was similar between groups (**Table 3**). Patients receiving phenobarbital also had greater benzodiazepine exposure before ICU admission and during ICU and hospital stay (**Table 4**). In the predefined Midwest subgroup, findings were consistent with the overall cohort. Phenobarbital was not associated with a statistically significant difference in time to hospital discharge (DRR, 0.98; 95% CI, 0.76–1.26; $p = 0.89$) or time to ICU discharge (DRR, 0.86; 95% CI, 0.65–1.15; $p = 0.31$), and rates of hypotension and intubation were similar between groups (**eTable 3**, <https://links.lww.com/CCX/B672>).

TABLE 1.
Baseline Demographics and Clinical Characteristics Before Propensity Score Matching

Variables	Total Patients (n = 1216)	Phenobarbital (n = 345)	Nonphenobarbital (n = 871)
Demographics			
Age	49.7 (14.2)	47.4 (12.9)	50.6 (14.6)
Gender, male	874 (71.9%)	283 (82.0%)	591 (67.9%)
Weight (kg)	83.8 (22.1)	85.2 (21.4)	83.3 (22.4)
Home medications			
Home benzodiazepine	145 (11.9%)	45 (13.0%)	100 (11.5%)
Home opioid	95 (7.8%)	16 (4.6%)	79 (9.1%)
Home phenobarbital	3 (0.2%)	2 (0.6%)	1 (0.1%)
Psychiatric comorbidities			
Depression	727 (59.8%)	190 (55.1%)	537 (61.7%)
Schizophrenia	28 (2.3%)	7 (2.0%)	21 (2.4%)
Bipolar disorder	176 (14.5%)	30 (8.7%)	146 (16.8%)
Psychotic disorder	164 (13.5%)	23 (6.7%)	141 (16.2%)
Medical comorbidities			
Hypertension	807 (66.4%)	235 (68.1%)	572 (65.7%)
Cerebrovascular disease	208 (17.1%)	49 (14.2%)	159 (18.3%)
Chronic obstructive pulmonary disease	217 (17.8%)	50 (14.5%)	167 (19.2%)
Chronic kidney disease	160 (13.2%)	42 (12.2%)	118 (13.5%)
Diabetes	237 (19.5%)	56 (16.2%)	181 (20.8%)
Alcoholic liver disease	1144 (94.1%)	324 (93.9%)	820 (94.1%)
Seizure disorder	342 (28.1%)	117 (33.9%)	225 (25.8%)
Delirium tremens	423 (34.8%)	164 (47.5%)	259 (29.7%)
Charlson Comorbidity Index	3.4 (3.1)	3.0 (3.0)	3.5 (3.1)
Baseline laboratory values and severity measures			
Serum ethanol	106.4 (140.5)	109.0 (143.0)	105.3 (139.6)
Aspartate aminotransferase (U/L)	184.6 (981.7)	143.1 (148.7)	201.3 (1158.8)
Alanine aminotransferase (U/L)	87.8 (261.2)	77.7 (73.1)	91.8 (305.8)
Total bilirubin (mg/dL)	1.8 (3.4)	1.6 (2.7)	1.9 (3.7)
CIWA at admission	16.4 (6.2)	17.4 (6.5)	16.0 (6.0)
CIWA at treatment	13.8 (8.3)	15.4 (10.7)	13.2 (7.1)
Acute Physiology and Chronic Health Evaluation III score	63.8 (28.2)	66.3 (27.3)	62.8 (28.5)
Cumulative lorazepam equivalents before ICU admission (mg)	7.6 (17.8)	14.2 (24.8)	4.9 (13.3)

CIWA = Clinical Institute Withdrawal Assessment.

Values reflect the unmatched cohort before propensity score matching. Missing data were as follows: weight, two total (one nonphenobarbital and one phenobarbital); serum ethanol, 299 total (225 nonphenobarbital and 74 phenobarbital); aspartate aminotransferase, 36 total (30 nonphenobarbital and six phenobarbital); alanine aminotransferase, 38 total (31 nonphenobarbital and seven phenobarbital); total bilirubin, 38 total (32 nonphenobarbital and six phenobarbital); CIWA for Alcohol, revised at treatment initiation, 74 total (46 nonphenobarbital and 28 phenobarbital); and Acute Physiology and Chronic Health Evaluation III score, three total (two nonphenobarbital and one phenobarbital).

Data are presented as mean (sd) or *n* (%), unless otherwise indicated.

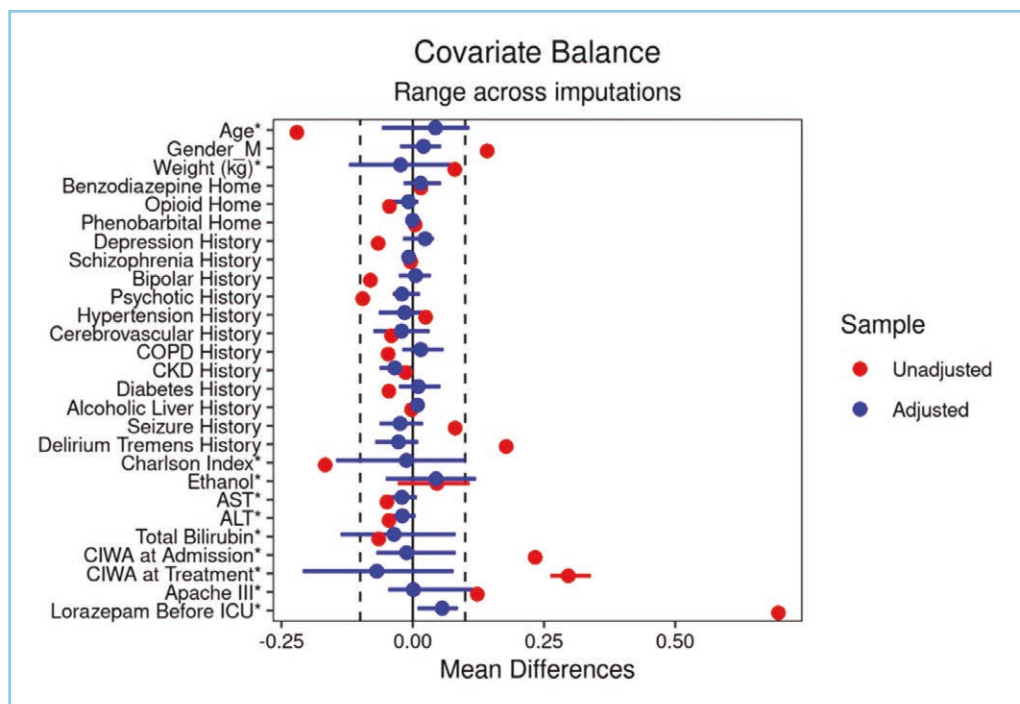


Figure 2. Covariate balance before and after propensity score matching across multiple imputations. *Love plot* showing standardized mean differences for baseline covariates before matching and after propensity score matching with weighting across imputed datasets. *Red points* indicate the unadjusted sample and *blue points* indicate the adjusted sample. *Vertical reference lines* at ± 0.1 indicate acceptable covariate balance. ALT = alanine aminotransferase, APACHE III = Acute Physiology and Chronic Health Evaluation III, AST = aspartate aminotransferase, CIWA = Clinical Institute Withdrawal Assessment, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease.

DISCUSSION

In this multicenter cohort of critically ill adults with AWS, phenobarbital use was consistent with a more severe, benzodiazepine-exposed treatment escalation pathway rather than a uniform treatment strategy. In adjusted ATC time-to-discharge models evaluating discharge alive from treatment initiation, phenobarbital was not associated with a statistically significant difference in time to hospital discharge or time to ICU discharge, although the ICU discharge estimate suggested a lower discharge rate that did not reach statistical significance. Adjusted odds of hypotension and intubation were similar between groups, whereas aspiration within 24 and 48 hours after treatment initiation was less frequent with phenobarbital. These findings suggest that phenobarbital use in real-world ICU practice has a similar early hemodynamic and respiratory safety profile, but its relationship with time to discharge is strongly shaped by treatment timing, withdrawal severity, and concomitant sedative exposure. In the predefined Midwest subgroup, findings were consistent

with the overall cohort. Phenobarbital was not associated with a statistically significant difference in time to hospital discharge (DRR, 0.98; 95% CI, 0.76–1.26; $p = 0.89$) or time to ICU discharge (DRR, 0.86; 95% CI, 0.65–1.15; $p = 0.31$), and rates of hypotension and intubation were similar between groups (eTable 3, <https://links.lww.com/CCX/B672>). Covariate balance after adjustment remained acceptable in the Midwest subgroup (eFig. 1, <https://links.lww.com/CCX/B672>).

A likely explanation for the observed treatment-context pattern is confounding by indication combined with heterogeneity in

treatment timing. Current guidance generally reserves phenobarbital for selected inpatients with severe withdrawal or as adjunctive therapy after adequate benzodiazepine treatment, particularly in closely monitored settings (14). In contrast, studies reporting shorter LOS with phenobarbital typically used early, protocolized, weight-based phenobarbital pathways that reduced concomitant benzodiazepine exposure (10, 15). In our cohort, patients who received phenobarbital had substantially greater benzodiazepine exposure before ICU admission and throughout the ICU stay, suggesting that phenobarbital was often used in patients with more severe or refractory withdrawal. Median pre-ICU lorazepam-equivalent exposure was higher in the phenobarbital group than in the nonphenobarbital group (4 mg [0–14.5 mg] vs. 0.2 mg [0–4 mg]), and this pattern was consistent through 48 hours after ICU admission (7 mg [0–23.5 mg] vs. 5 mg [1–15 mg]) and across the ICU stay overall (10.5 mg [1–38 mg] vs. 5.5 mg [1–16 mg]). These findings suggest that phenobarbital was often used as an escalation or rescue

TABLE 2.**Adjusted Average Treatment Effect in the Control Outcome Models for Time to Discharge Alive and Safety Outcomes**

Outcome	Estimate (95% CI)	<i>p</i>
Time to hospital discharge alive	DRR, 0.91 (0.74–1.12)	0.37
Time to ICU discharge alive	DRR, 0.77 (0.59–1.01)	0.057
Mean arterial pressure < 65 mm Hg	OR, 0.79 (0.47–1.33)	0.376
Intubation	OR, 0.57 (0.16–2.09)	0.396

DRR = discharge rate ratio, OR = odds ratio.

Estimates are shown for phenobarbital relative to nonphenobarbital regimens. Time-to-discharge outcomes were modeled from treatment initiation using Poisson regression models with discharge alive as the event and are reported as DRRs. A DRR < 1 indicates a lower rate of discharge alive and therefore longer time to discharge. Patients who died before discharge were censored at death, and mortality was reported separately. Binary outcomes are reported as ORs.

TABLE 3.**Secondary Clinical Outcomes After Treatment Initiation**

Outcome	Phenobarbital (<i>n</i> = 345)	Nonphenobarbital (<i>n</i> = 871)	<i>p</i>
Aspiration outcomes			
Aspiration within 24 hr	26/345 (7.5%)	107/871 (12.3%)	0.017 ^a
Aspiration within 48 hr	27/345 (7.8%)	110/871 (12.6%)	0.017 ^a
CIWA-Ar change outcomes			
CIWA-Ar change to 24 hr	6.6 (10.6)	5.6 (8.2)	0.820
CIWA-Ar change to 48 hr	7.8 (12.3)	6.6 (9.1)	0.926
CIWA-Ar change from 24 to 48 hr	1.4 (6.1)	1.3 (7.3)	0.910

CIWA-Ar = Clinical Institute Withdrawal Assessment for Alcohol, revised.

^aThe *p* values for aspiration within 24 and 48 hr were identical after rounding to three decimal places.

Missing data: CIWA-Ar at 24 hr was missing for 241 patients (166 nonphenobarbital; 75 phenobarbital), and CIWA-Ar at 48 hr was missing for 398 patients (303 nonphenobarbital; 95 phenobarbital).

Data are presented as *n/N* (%) or mean (sd), as appropriate.

TABLE 4.**Cumulative Benzodiazepine and Phenobarbital Exposure Over Time**

Outcome/Timepoint	Nonphenobarbital (<i>n</i> = 871)	Phenobarbital (<i>n</i> = 345)
LE before ICU admission (mg)	0.2 (0–4)	4 (0–14.5)
LE from ICU admission to 48 hr (mg)	5 (1–15)	7 (0–23.5)
LE total during ICU stay (mg)	5.5 (1–16)	10.5 (1–38)
LE total at hospital discharge (mg)	8 (2–22.5)	13.5 (2–48)
Phenobarbital total at 0–48 hr (mg)	–	648 (390–1065)
Phenobarbital total at ICU discharge (mg)	–	715 (400–1235)
Phenobarbital total at hospital discharge (mg)	–	745 (410–1257)

LE = lorazepam equivalent.

Dashes indicate not applicable. Patients in the nonphenobarbital group did not receive phenobarbital.

Data are presented as median (interquartile range).

therapy rather than as an early standardized first-line strategy. Since phenobarbital exposure included any administration after T0, later initiation may have reflected patients who were already following a more severe or prolonged ICU trajectory.

The trend toward longer time to ICU discharge, without a significant difference in hospital discharge, is clinically plausible given phenobarbital pharmacokinetics and concomitant sedative exposure. Phenobarbital is a long-acting barbiturate with an adult half-life of roughly 50–150 hours, and its CNS-depressant effects can be additive with other sedatives (14, 16). In a cohort such as ours, where the phenobarbital group also received substantially more benzodiazepines, this greater cumulative sedative burden may have delayed normalization of mental status, de-escalation of monitoring, or readiness for transfer and discharge, even without increasing early hypotension or intubation (17). At the same time, the lower aspiration rate suggests that once phenobarbital was introduced, it may have provided more durable control of agitation and emesis, thereby potentially reducing airway related complications despite a more severe overall withdrawal trajectory.

To our knowledge, direct comparisons of phenobarbital-based and nonphenobarbital strategies in real-world ICU cohorts of patients with AWS remain limited. However, some studies suggest that early, structured phenobarbital pathways may improve outcomes in severe withdrawal, including lower ICU utilization, faster symptom control, less mechanical ventilation, and shorter LOS. For example, Rosenson et al (18) reported fewer ICU admissions with a single IV phenobarbital dose added to symptom-triggered lorazepam, and Tidwell et al (19) found shorter ICU stay and lower rates of mechanical ventilation with a rapid phenobarbital-loading protocol (11). At the same time, the literature has not been uniformly favorable. Other studies have shown that when phenobarbital is introduced later, used adjunctively, or given in populations already receiving substantial benzodiazepine exposure, the benefits are less consistent and may be accompanied by longer hospitalization or higher rates of mechanical ventilation. This pattern has been reported in multicenter, emergency department, and neurocritical care cohorts, including studies by Cheng et al (17), Norris et al (20), and Sullivan et al (21). Our findings align more closely with this latter body of literature.

In our cohort, phenobarbital was not associated with a statistically significant difference in time to ICU or hospital discharge in adjusted time-to-discharge models, whereas early hypotension and intubation were similar and aspiration was less frequent. Phenobarbital exposure alone does not fully explain the observed time-to-discharge findings, which were also shaped by the clinical context in which phenobarbital was used in routine ICU practice. These contextual factors include timing of initiation, degree of protocolization, patient selection, and concomitant benzodiazepine exposure as demonstrated by the previous studies (9, 17, 20–22), which differs from the early, protocolized pathways reported in more favorable studies. In this context, phenobarbital may be most beneficial when used early and in a standardized manner. By contrast, when phenobarbital is started later and used without a standardized approach in patients who are already on a more severe course, it may retain some early safety benefits but may not shorten LOS. These results suggest that in ICU AWS, the observed association of phenobarbital use is shaped more by timing, treatment standardization, and patient selection than by phenobarbital exposure alone.

This study has several notable strengths. It evaluates phenobarbital in a pragmatic, ICU-focused cohort that more closely reflects routine clinical practice than many prior studies, which have often come from single-center protocol studies or settings with more standardized phenobarbital use. By comparing phenobarbital-based and nonphenobarbital strategies in patients managed within the same health system and with access to similar adjunctive agents, including benzodiazepines, dexmedetomidine, and propofol, our analysis better captures contemporary ICU escalation pathways for severe AWS. The use of multiple imputation and propensity score matching within an ATC framework also strengthened the analysis by improving comparability between groups while preserving the analytic sample. In addition, the time-to-discharge analysis began follow-up at treatment initiation and reported mortality separately, which helped reduce bias from pretreatment observation time and improved interpretation of discharge outcomes. As such, this real-world study complements prior work that has reported favorable outcomes with more structured phenobarbital pathways.

These findings should be interpreted in the context of several limitations. First, this was a retrospective

observational study and therefore residual confounding by indication likely remained despite multiple imputation, propensity score matching, and improved measured covariate balance. Patients who received phenobarbital had markers of more severe or refractory withdrawal and greater benzodiazepine exposure before and during ICU care, suggesting that phenobarbital was often used as escalation therapy rather than as an early standardized strategy. Post-treatment benzodiazepine exposure and adjunctive sedative use were not included as baseline propensity covariates because they may represent downstream treatment escalation. Therefore, these findings should not be interpreted as a causal effect of phenobarbital itself.

Second, phenobarbital use was not standardized across sites. Some centers had formal guidance, whereas others relied on clinician discretion, and differences in dosing and timing likely introduced treatment heterogeneity. Although phenobarbital was often started early after ICU admission, the broad range in time to initiation suggests that timing varied across patients and may have influenced outcomes. Additionally, starting follow-up at treatment initiation reduced pre-treatment immortal-time bias; however, this approach may not fully eliminate time-dependent exposure bias because phenobarbital could still be introduced as escalation in response to evolving clinical status. In addition, patients who died before discharge were censored in the time-to-discharge models, and mortality was reported separately; formal competing-risk estimates of discharge probability were not generated.

Third, treatment exposure could not be fully characterized. Phenobarbital use before ICU admission was not captured, whereas pre-ICU benzodiazepine exposure was available. Detailed dosing and timing of adjunctive sedatives other than benzodiazepines and phenobarbital were not fully captured, limiting our ability to distinguish specific nonphenobarbital treatment patterns. Although cumulative phenobarbital exposure was summarized using median and interquartile range, weight-standardized dosing and dose intensity over time, such as mg/kg or mg/kg/d, were not available. Cumulative exposure should therefore be interpreted descriptively because total dose may be influenced by duration of ICU or hospital stay.

Other limitations include incomplete CIWA-Ar documentation at 24 and 48 hours, making symptom-response analyses exploratory, and reliance

on electronic documentation and ICD coding for comorbidity and outcome ascertainment. The study also overlapped with the COVID-19 pandemic, when sedation practices and ICU workflows may have shifted. Finally, although the study included multiple sites, it was conducted within a single integrated health system, and residual site-level differences in ICU practice, staffing, step-down availability, and discharge processes may limit generalizability.

Accordingly, our findings should be viewed as real-world data on how phenobarbital is used in ICU AWS practice, especially as part of treatment escalation, rather than as proof of a consistent treatment effect across all settings.

CONCLUSIONS

In this multicenter ICU cohort, phenobarbital use was consistent with a more severe, benzodiazepine-exposed treatment-escalation pathway rather than a uniform treatment strategy. In adjusted time-to-discharge models from treatment initiation, phenobarbital was not associated with a statistically significant difference in time to ICU or hospital discharge alive. Early hypotension and intubation were similar between groups, and aspiration was less frequent with phenobarbital. Prospective, protocolized studies are needed to define optimal timing, dosing, and patient selection.

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