

Original Contributions

PHENOBARBITAL FOR ACUTE ALCOHOL WITHDRAWAL: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

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□ **Abstract—Background:** Acute alcohol withdrawal syndrome (AAWS) is encountered in patients presenting acutely to the Emergency Department (ED) and often requires pharmacologic management. **Objective:** We investigated whether a single dose of intravenous (i.v.) phenobarbital combined with a standardized lorazepam-based alcohol withdrawal protocol decreases intensive care unit (ICU) admission in ED patients with acute alcohol withdrawal. **Methods:** This was a prospective, randomized, double-blind, placebo-controlled study. Patients were randomized to receive either a single dose of i.v. phenobarbital (10 mg/kg in 100 mL normal saline) or placebo (100 mL normal saline). All patients were placed on the institutional symptom-guided lorazepam-based alcohol withdrawal protocol. The primary outcome was initial level of hospital admission (ICU vs. telemetry vs. floor ward). **Results:** There were 198 patients enrolled in the study, and 102 met inclusion criteria for analysis. Fifty-one patients received phenobarbital and 51 received placebo. Baseline characteristics and severity were similar in both groups. Patients that received phenobarbital had fewer ICU admissions (8% vs. 25%, 95% confidence interval 4–32). There were no differences in adverse events. **Conclusions:** A single dose of i.v. phenobarbital combined with a symptom-guided lorazepam-based alcohol withdrawal protocol resulted in decreased ICU admission and did not cause increased adverse outcomes. © 2013 Elsevier Inc.

□ **Keywords—alcohol withdrawal; emergency medicine; ICU; lorazepam; phenobarbital**

INTRODUCTION

Background

Small studies have investigated use of phenobarbital for treatment of acute alcohol withdrawal (1–3). The longer half-life of phenobarbital compared to lorazepam may be a clinical advantage in the treatment of acute alcohol withdrawal (4). The lack of prospective data regarding use of phenobarbital for alcohol withdrawal leaves clinicians basing their use of phenobarbital for acute alcohol withdrawal on limited or anecdotal evidence.

Importance

Acute alcohol withdrawal is encountered in patients presenting acutely to the Emergency Department (ED). There are likely in excess of 8 million alcohol-dependent people in the United States; every year, approximately 500,000 episodes of acute alcohol withdrawal syndrome (AAWS) require pharmacologic management (5). AAWS results in a significant utilization of health care resources,

particularly in safety-net and emergency health care settings.

Goals of This Investigation

We hypothesized that a single dose of intravenous (i.v.) phenobarbital combined with a standardized, symptom-guided lorazepam-based alcohol withdrawal protocol would result in decreased intensive care unit (ICU) admission.

MATERIALS AND METHODS

Study Design

This was a prospective, randomized, double-blind, placebo-controlled study of ED patients with AAWS admitted to the hospital with a primary admission diagnosis of alcohol withdrawal (International Classification of Diseases, 9th Revision [ICD-9] code 291.81). All study investigators, enrolling providers, nursing staff, statisticians, and research assistants were blinded to group allocation for the duration of the study. Unblinding occurred after completion of data analysis. The study institution Committee for the Protection of Human Subjects and study investigators produced a consent procedure based on prior studies investigating treatment of AAWS and associated complications (6,7). The study Institutional Review Board (IRB) approved the study (ClinicalTrials.gov NCT 01884417).

Setting

The study took place in an urban ED with an annual census of 85,000 patients and a postgraduate year 1–4 Emergency Medicine residency program with 17 attending Emergency Physicians, 12 ED mid-level practitioners (MLPs), and 40 Emergency Medicine residents.

Selection of Participants

All patients over age 18 years presenting to the ED with suspected AAWS were evaluated by the enrolling attending Emergency Physician, MLP, or resident for participation in the study (all MLPs and residents were supervised by an attending Emergency Physician, and all patients were evaluated and examined by the attending physician). Inclusion criteria included provider judgment of clinical need for placement on the institutional lorazepam-based alcohol withdrawal protocol, clinical evidence of AAWS (including tachycardia [heart rate >100 beats/min], tremor, paroxysmal sweats, agitation, anxiety, hallucinations, or clouded sensorium) and provider judgment of anticipated need for hospital admis-

sion for inpatient management of AAWS (primary admission diagnosis ICD-9 Code 291.81). The study took place between January 2009 and March 2010 (Figure 1).

Exclusion criteria included age <18 years; pregnancy; allergy to phenobarbital, lorazepam, phenytoin, or carbamazepine; known severe hepatic impairment; inability to obtain i.v. access; and primary admission diagnosis other than acute alcohol withdrawal (ICD-9 Code 291.81).

Written informed consent was obtained from all study participants using a standardized consent form. Consent was initially waived for patients who were unable to give informed consent at the time of presentation due to intoxication or altered mental status. Once the patient became alert and demonstrated decision-making capacity, written consent was required for the continued collection of data; a post-waiver consent form was made available to these patients for this purpose. The rationale for waiver of initial consent is that all patients presenting with AAWS who were enrolled in the study were placed on the institution's lorazepam-based alcohol withdrawal protocol, an accepted standard-of-care treatment strategy for management of AAWS regardless of administration of additional agents used in the management of AAWS, such as phenobarbital or normal saline (8). Additionally, our institutional lorazepam-based alcohol withdrawal protocol is typically initiated without special consent of patients placed on the protocol for AAWS.

Randomization occurred in the Pharmacy Department using a random number-generator program without block randomization.

Interventions

All study participants were placed on the institutional symptom-guided lorazepam-based alcohol withdrawal protocol, a modified version of the Clinical Institute Withdrawal Assessment (CIWA) protocol. This protocol is applied globally for all patients admitted to the study hospital for treatment of AAWS (see Appendix 1 and 2 for Protocol forms). Patients were randomized to receive either a single dose of i.v. phenobarbital (10 mg/kg in 100 mL normal saline) or 100 mL normal saline, both delivered as clear solutions in same-sized, identical-appearing covered plastic bags, prepared by the pharmacy and infused over 30 min. The enrolling provider estimated patient weight. The study medication was requested from the pharmacy at the same time the alcohol withdrawal protocol was initiated. All study patients were placed on a cardiac monitor with continuous pulse oximetry while in the ED.

Methods of Measurement

Time of arrival in the ED, initial vital signs, initial Alcohol Withdrawal Clinical Assessment (AWCA) score, timing

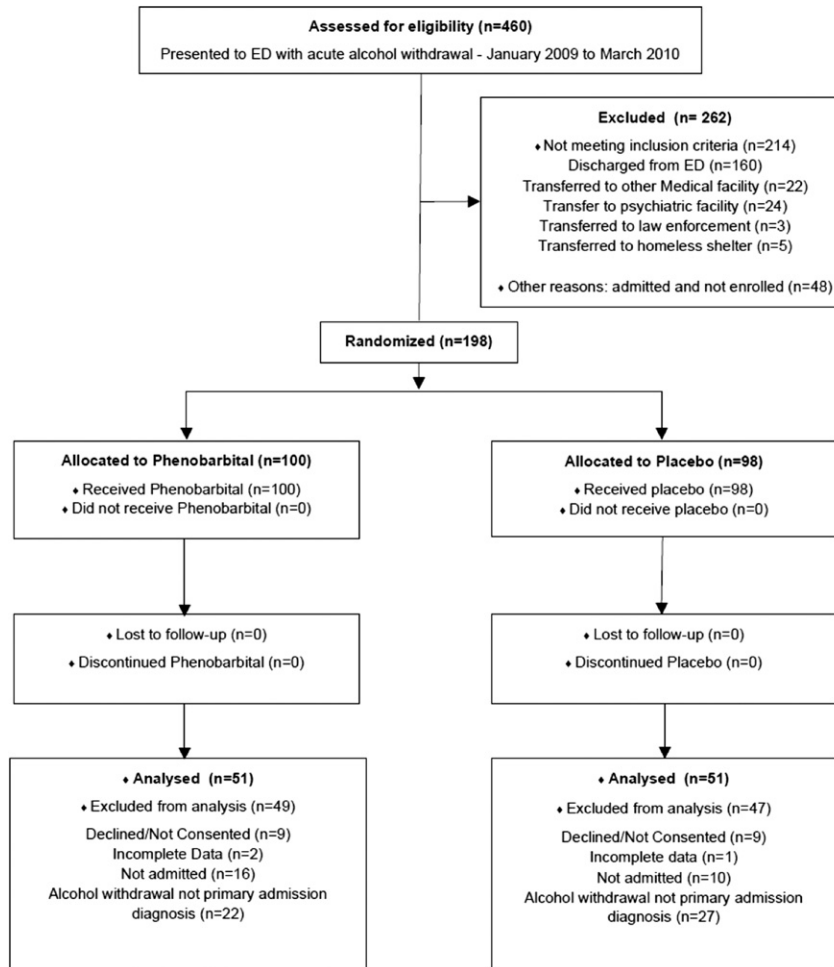


Figure 1. Study flowchart. ED = Emergency Department.

of initial lorazepam and study medication administration, timing of hospital admission (defined as the time admission orders were documented by the admitting team), initial and subsequent level of hospital care (ICU [nurse: patient ratio = 1:2] vs. telemetry [nurse: patient ratio = 1:3] vs. floor ward [nurse: patient ratio = 1:4]), maximum AWCA score, time of discharge, and prior AAWS hospital admissions were obtained from either the ED Wellsoft (Wellsoft Corporation, Somerset, NJ) medical record system, the hospital OAS Gold (Siemens Corporation, Washington, DC) medical record system, or the paper chart. Medication data including routes of administration were obtained from the pharmacy Pyxis system (Care Fusion, San Diego, CA). Incidence of seizures, intubation, falls, use of mechanical restraints, need for bedside sitter, and mortality were obtained from the medical record.

Outcome Measures

The primary outcome measure was initial level of hospital admission from the ED. Use of continuous lorazepam

infusion, time from hospital admission to discharge (length of stay [LOS] in hours), total amount of lorazepam used per patient, and incidence of adverse events were also assessed.

Primary Data Analysis

Trained research assistants and study investigators extracted data from the electronic record system or hospital chart. The Pharmacy Department extracted medication data from the hospital Pyxis system. All study data were recorded on a standardized data collection instrument and stored in Excel (Version 11.5.8; Microsoft Corporation, Redmond, WA). Inter-rater reliability was evaluated by re-examination of data from 30 randomly selected study patients; agreement was 100% on all data points. Statistical software (Stata Version 10.0 [StataCorp LP, College Station, TX] and Mathematica Version 7.0 [Wolfram Research Inc., Champaign, IL]) was used to calculate study statistics, including pre-specified two-sided testing of median values and interquartile

range with two-sample Wilcoxon rank-sum test for non-normally distributed outcomes and mean values and SD, two-sample Student's *t*-test for normally distributed continuous outcomes. We analyzed discrete variables, including the primary outcome, with the chi-squared test, assuming significance at the $p \leq 0.05$ level. Total study enrollment was limited by feasibility (1-year enrollment period) and formal sample size analysis was not done.

RESULTS

During the study period from January 2009 to March 2010, 460 patients presented to the ED with acute alcohol withdrawal. There were 198 patients enrolled during the study period, and 102 met inclusion criteria for analysis. Thirty subjects (59%) in the phenobarbital group and 32 patients (63%) in the placebo group initially waived consent and were subsequently consented and included in the analysis (Figure 1).

Fifty-one patients were randomized to receive phenobarbital and 51 received placebo. There were no baseline differences between the two groups (Table 1).

Patients receiving a single dose of i.v. phenobarbital had a decreased ICU admission rate (phenobarbital vs. placebo, 8% vs. 25%, difference 17% [95% confidence interval (CI) 4–32%]). There were no differences in telemetry admission, floor ward admission, and median ICU or total hospital LOS. After admission, no study patients were transferred to a higher level of inpatient care.

There were no differences in incidence of adverse outcomes, including intubation, seizure, mechanical restraints, and bedside sitter. There were no falls or mortality reported in either group.

Phenobarbital resulted in decreased use of continuous lorazepam infusion (4% vs. 31%; difference 27% [95% CI 14–41%]) and decreased total lorazepam required (26 vs. 49 mg; difference 23 mg [95% CI 7–40]) (Table 2). There were no differences in administration

of other medications, including morphine, fentanyl, hydromorphone, propofol, and haloperidol (Table 3).

DISCUSSION

A single dose of i.v. phenobarbital resulted in decreased ICU admission rate, decreased use of continuous lorazepam infusion, and was not associated with increased adverse events. Phenobarbital has been cited as a second-line agent for AAWS and other conditions for which benzodiazepines are considered first-line treatment, such as status epilepticus. Our study provides further evidence to support use of phenobarbital as an adjunct to benzodiazepines for AAWS and also provides evidence that phenobarbital and lorazepam may have synergistic clinical effects when used for AAWS.

Phenobarbital is a central nervous system depressant active in the cuneate nucleus, substantia nigra, and thalamic relay neurons. Phenobarbital's mechanism of action is mediated by gamma aminobutyric acid (GABA) at the GABA (A) receptor and is different from that of GABA itself, the benzodiazepines, and the ultra short-acting barbiturates (4). Benzodiazepines increase the frequency of chloride channel opening caused by GABA (A) receptor activation, requiring the presence of pre-synaptic GABA, whereas phenobarbital enhances GABA (A) chloride currents by increasing the duration of chloride channel opening (9). The half-life of phenobarbital is 80–120 h, whereas the half-life of lorazepam is significantly less at 14–20 h; the duration of sedation of phenobarbital is 4–10 h, compared to lorazepam at 6–8 h (4).

This study raises areas for future research. Repeating the trial in multiple centers to achieve greater statistical power is necessary to prospectively validate our results. A comparison of symptom-guided phenobarbital vs. symptom-guided lorazepam for AAWS in ED patients would address the question of which agent is superior

Table 1. Baseline Characteristics of Study Patients

Subject Descriptor*	Phenobarbital (n = 51)	Placebo (n = 51)
Male: n (%)	46 (90)	45 (88)
Age, years: median (IQR)	46 (40–52)	48 (37–54)
Initial AWCA score: median (IQR)	6 (4–10)	7 (4–10)
Initial heart rate: median (IQR)	106 (100–123)	112 (108–120)
Initial tremor: n (%)	48 (95)	48 (95)
Initial sweats: n (%)	25 (49)	32 (63)
Initial agitation: n (%)	20 (40)	21 (41)
Initial anxiety: n (%)	35 (68)	43 (84)
Altered level of consciousness: n (%)	30 (58)	35 (68)
Auditory/visual disturbances: n (%)	20 (40)	21 (41)
Time to initial lorazepam administration, minutes: median (IQR)	84 (48–146)	84 (40–312)
Time to study medication administration, minutes: median (IQR)	144 (103–263)	150 (100–264)
Patients with prior alcohol withdrawal admissions to study institution: n (%)	21 (41)	25 (49)

IQR = interquartile range; AWCA = Alcohol Withdrawal Clinical Assessment.

* No significant difference between groups for any measured demographic.

Table 2. Clinical Outcomes

Clinical Outcome*	Phenobarbital (n = 51)	Placebo (n = 51)	Difference (95% CI)
ICU admission: n (%)	4 (8)	13 (25)	17 (4–32)
TCU admission, number: n (%)	23 (45)	20 (39)	–6 (–25–13)
Floor admission: n (%)	24 (47)	18 (35)	–12 (–31–7)
Maximum AWCA score: median (IQR)	8 (5–10)	10 (5–14)	2 (–0.2–3)
Continuous lorazepam infusion: n (%)	2 (4)	16 (31)	27 (14–41)
Total length of stay, hours: median (IQR)	76 (54–114)	118 (47–190)	42 (–4–82)
ICU length of stay, hours: median (IQR)	34 (30–276)	94 (43–134)	60 (–170–434)
Intubation: n (%)	1 (2)	1 (2)	0 (–0.05–0.05)
Seizure: n (%)	1 (2)	2 (4)	2 (–5–9)
Restraints: n (%)	15 (29)	23 (45)	16 (–3–34)
Bedside sitter: n (%)	14 (28)	11 (22)	–6 (–11–23)

CI = confidence interval; ICU = intensive care unit; TCU = transitional care unit; AWCA = Alcohol Withdrawal Clinical Assessment; IQR = interquartile range.

* No falls nor mortalities were observed in any study subjects.

monotherapy for this purpose—use of aliquots of phenobarbital, titrated in increments of 130–260 mg i.v. to effect of somnolence up to a maximum dose of 1040 mg for AAWS is a strategy used in our ED and others before this study (3). Accurate early identification of which ED patients are at highest risk of severe, refractory AAWS, necessitating ICU admission or continuous lorazepam infusion, is an area of research that could allow targeted use of phenobarbital in patients most likely to benefit from this treatment.

We did not do a cost-benefit analysis in our study; however, the implication of preventing ICU admission by an intervention such as 10 mg/kg of i.v. phenobarbital, which costs our institution approximately \$18.00 for a 70-kg adult, is significant. Given the morbidity, mortality, and financial cost burden of alcohol withdrawal, the potential benefit of i.v. phenobarbital warrants further study.

Limitations

The decision to enroll ED patients in the study relied on ED provider judgment of the anticipated need for hospital admission for a primary admission diagnosis of acute alcohol withdrawal (ICD-9 Code 291.81). In addition to the 102 patients randomized and included in our analysis, 48 patients were admitted to the hospital with a primary diagnosis of acute alcohol withdrawal during the study period and not enrolled in the study (16 ICU, 18 telemetry, and 14 floor ward). These patients may have been appropriate for enrollment in the study and their absence may have affected our results. Of these 48 non-enrolled admitted patients, none of the 16 admitted to the ICU received phenobarbital in addition to lorazepam in the ED, and of these 16 ICU patients, 13/16 (81%) required continuous lorazepam infusion. The incidence of ICU admission and continuous lorazepam infusion seems

Table 3. Medication Results

Medications	Medication Statistics	Phenobarbital (n = 51)	Placebo (n = 51)	Difference (95% CI)
Phenobarbital i.v. (mg)	Patients receiving medication: n (%)	4 (8)	5 (10)	142 (–20–303)
	mean dose (SD)	62 (253)	204 (514)	
Phenobarbital p.o. (mg)	Patients receiving medication: n (%)	0 (0)	3 (6)	43 (–36–121)
	mean dose (SD)	0 (0)	43 (179)	
Lorazepam i.v. (mg)	Patients receiving medication: n (%)	42 (82)	49 (96)	23 (7–40)
	mean dose (SD)	26 (45)	49 (37)	
Lorazepam p.o. (mg)	Patients receiving medication: n (%)	2 (4)	1 (2)	–1 (–4–2)
	mean dose (SD)	2 (11)	1 (2)	
Morphine i.v. (mg)	Patients receiving medication: n (%)	12 (24)	11 (22)	4 (–14–5)
	mean dose (SD)	11 (17)	15 (31)	
Fentanyl i.v. (μg)	Patients receiving medication: n (%)	8 (16)	13 (26)	42 (–13–97)
	mean dose (SD)	10 (32)	52 (194)	
Hydromorphone i.v. (mg)	Patients receiving medication: n (%)	5 (10)	3 (6)	–1 (–3–0.5)
	mean dose (SD)	1 (6)	0 (0.7)	
Propofol i.v. (mg)	Patients receiving medication: n (%)	2 (4)	0 (0)	–32 (–83–19)
	mean dose (SD)	32 (178)	0 (0)	
Haloperidol p.o./i.v. (mg)	Patients receiving medication: n (%)	0 (0)	2 (4)	0.5 (–2–0.5)
	mean dose (SD)	0 (0)	0.5 (4)	

CI = confidence interval.

consistent with our result in the placebo group, suggesting that the absence of these patients from the study population biases our result to the null, rather than exaggerating the effect on our results. We did not assess whether bed availability affected level of inpatient disposition, which may limit our results.

The study was done in a single county ED, using our institutional alcohol withdrawal protocol based on CIWA-Ar (Clinical Institute Withdrawal Assessment—Alcohol, revised); our results may not be applicable to other institutions using a different alcohol withdrawal protocol. The AWCA scale used in our study was developed by the medical director of the study institution ICU as a simplified version of the CIWA-Ar. Although there is evidence that similar scoring systems using a subset of the 10 CIWA-Ar parameters are effective for evaluation and treatment of AAWS, the AWCA used in this study is unvalidated and may limit our results (10). Inter-rater reliability was not assessed regarding AWCA scores, possibly limiting our results.

Use of continuous lorazepam infusion mandates ICU admission in the study institution. Aside from continuous vasoactive, sedative, or insulin infusion and requirement for mechanical ventilation, there is not a formal set of criteria that define the need for ICU admission in the study institution. We did not ask enrolling ED providers to change their admission criteria, clinical judgment, or decision-making regarding inpatient disposition for study purposes—the decision to admit a patient to the ICU or to implement continuous lorazepam infusion was based on provider judgment rather than a standardized protocol, and may also limit generalizing our results. The lack of formally assessed inter-rater reliability regarding ICU admission is a significant limitation of our study.

Our study protocol of 10 mg/kg of phenobarbital was the largest dose approved by the study institution IRB and may not be the optimal regimen that avoids both over-sedation and under-medication for AAWS. Patient weight was estimated and may have led to variability of phenobarbital dosing. Study patients were predominantly

male. Lack of sample size analysis limits extrapolation of the observed differences between groups.

CONCLUSIONS

A single dose of i.v. phenobarbital resulted in decreased ICU admission rate, decreased use of continuous lorazepam infusion, and was not associated with increased adverse events. Given the morbidity, mortality, and financial cost burden of acute alcohol withdrawal, the potential benefit of i.v. phenobarbital for AAWS warrants further study.

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ARTICLE SUMMARY

1. Why is this topic important?

Acute alcohol withdrawal syndrome is encountered in patients presenting acutely to the Emergency Department (ED) and often requires pharmacologic management.

2. What does this study attempt to show?

We investigate whether a single dose of intravenous phenobarbital combined with a standardized lorazepam-based alcohol withdrawal protocol decreases intensive care unit (ICU) admission in ED patients with acute alcohol withdrawal.

3. What are the key findings?

There were 198 patients enrolled in the study, and 102 met inclusion criteria for analysis. Fifty-one patients received phenobarbital and 51 received placebo. Baseline characteristics and severity were similar in both groups. Patients that received phenobarbital had fewer ICU admissions (8% vs. 25%, 95% confidence interval 4–32). There were no differences in adverse events.

4. How is patient care impacted?

Phenobarbital is an option for treatment of acute alcohol withdrawal in ED patients. Phenobarbital may decrease ICU admission and does not seem to increase adverse events.

ACUTE ALCOHOL WITHDRAWAL Physician Orders

Check **both assessment and medication orders for A, B, and C** (all are required).
Oral administration is the preferred route.

A. Withdrawal Prophylaxis – Alcohol Withdrawal Clinical Assessment (AWCA) Score < 3			
<input type="checkbox"/> • Assess AWCA & Sedation Scale q6h. <input type="checkbox"/> • Assess Sedation Scale 1 hour after administration of PO Lorazepam. <input type="checkbox"/> • Assess Sedation Scale 15 minutes after IV or IM Lorazepam. <input type="checkbox"/> • For Sedation Scale > 2, assess vital signs, hold medication and notify HO. <input type="checkbox"/> • For AWCA ≥ 3, follow orders for "Mild-Moderate Acute Withdrawal" below.			
Lorazepam	<input type="checkbox"/> 1 mg <input type="checkbox"/> 2 mg <input type="checkbox"/> ___ mg	<input type="checkbox"/> PO <input type="checkbox"/> IM <input type="checkbox"/> IV	<input type="checkbox"/> x1 PRN <input type="checkbox"/> q6h around the clock <input type="checkbox"/> q6h PRN mild agitation <input type="checkbox"/> and x 1 PRN for AWCA ≥ 3, notify HO

B. Mild – Moderate Acute Withdrawal (AWCA Score ≥ 3 ≤ 10)			
<input type="checkbox"/> • Assess AWCA & Sedation Scale q4h. <input type="checkbox"/> • Assess Sedation Scale 1 hour after administration of PO Lorazepam. <input type="checkbox"/> • Assess Sedation Scale 15 minutes after IV or IM Lorazepam. <input type="checkbox"/> • For Sedation Scale > 2, assess vital signs, hold medication and notify HO. <input type="checkbox"/> • If AWCA < 3, follow order for "Withdrawal Prophylaxis" above. <input type="checkbox"/> • If AWCA > 10, follow orders for "Severe Withdrawal" below, and call HO to evaluate patient.			
Lorazepam	<input type="checkbox"/> 1 mg <input type="checkbox"/> 2 mg <input type="checkbox"/> ___ mg	<input type="checkbox"/> PO <input type="checkbox"/> IM <input type="checkbox"/> IV	<input type="checkbox"/> q 1 h x 2 PRN for AWCA ≥ 3, then q4h, titrating to Sedation Scale 1-2

C. Severe Acute Withdrawal (AWCA Score > 10)			
Note: Requires TCU, ICU, ED, or floor bed with telemetry and pulse oximetry.			
<input type="checkbox"/> • Assess Vital Signs, AWCA & Sedation Scale q2h. <input type="checkbox"/> • Continuous respiratory/O ₂ sat monitoring. Notify HO if RR < 8 or O ₂ sat < 90%. <input type="checkbox"/> • Assess Sedation Scale 15 minutes after each dose of IV Lorazepam. <input type="checkbox"/> • For sedation score > 2, hold medication. <input type="checkbox"/> • If AWCA < 10, refer to treatment orders for "Mild-Moderate Acute Withdrawal" above.			
Lorazepam	<input type="checkbox"/> 2 mg <input type="checkbox"/> 3 mg <input type="checkbox"/> 4 mg <input type="checkbox"/> ___ mg	<input type="checkbox"/> IV	<input type="checkbox"/> q15-30 minutes, titrating to Sedation Scale 1-2.

Date: _____ Time: _____ Physician: _____ ID#: _____
(print name) (signature)

Date: _____ Time: _____ RN Signature: _____