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Treatment of Alcohol Withdrawal and Delirium Tremens

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". . . drunkenness brings pallor and sagging cheeks, sore eyes, and trembling hands that spill a full cup, of which the immediate punishment is a haunted sleep and unrestful nights. . ."

Pliny the Elder- 1st century BC

Get Ready for the Winter

US Alcohol Sales up 240% with COVID!

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What is not on Tap?

- Outpatient detoxification
- Outpatient withdrawal
- Other complications of Alcohol Abuse

It is more common than you think!

- 2-4% of US population with self reported AWS (NIAAA 1995)
- 8% of all Hospital Admissions have AWS
- 16% of post-surgical patients
- 31% of Trauma patients
  - Alcohol involved in 86% homicides
  - 25-35% MVAs
- Presence of AWS can increase mortality 3 fold

Definitions

Table 1. *DSM-IV* Diagnostic Criteria for Alcohol Withdrawal and Alcohol Withdrawal Delirium*

Alcohol Withdrawal

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after criterion A:
   (1) Autonomic hyperactivity (eg, sweating or pulse rate >100/min)
   (2) Increased hand tremor
   (3) Insomnia
   (4) Nausea or vomiting
   (5) Transient visual, tactile, or auditory hallucinations or illusions
   (6) Psychomotor agitation
   (7) Anxiety
   (8) Grand mal seizures
C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.
   Specify whether with perceptual disturbances.

Alcohol Withdrawal Delirium†

A. Disturbance of consciousness (ie, reduced clarity of awareness of the environment), with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (such as memory deficit, disorientation, or language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
C. The disturbance develops in a short period (usually hours to days) and tends to fluctuate during the day.
D. There is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria A and B developed during, or shortly after, a withdrawal syndrome.

OHSU
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Early Uncomplicated AWS

- Begins as early as 6hrs after cessation
- “Morning shakes” and “Eye opener”
- Mild autonomic hypereactivity
  - Hypertension, tachycardia
- Can be treated with ETOH (self treatment)

Alcoholic Hallucinosis

- Affects up to 25% of AWS
- All types of Hallucinations reported
- Formication/Tactile very common
  - Not specific for AWS
- Associated with clear sensorium (if not then DTs)
- Does not predict the development of DTs

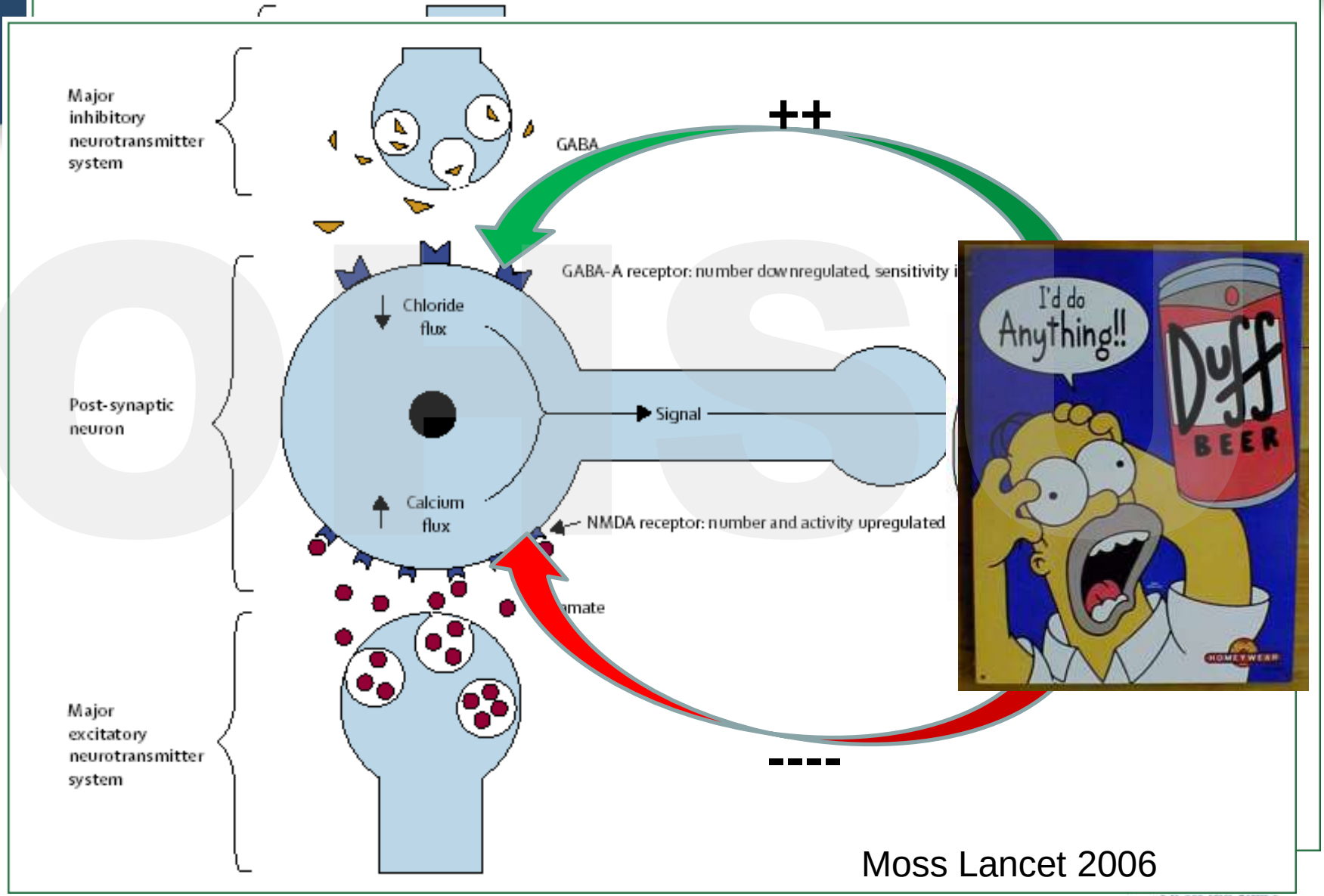
Alcohol Withdrawal Seizures

- Affects 10% of AWS
- Does not predict development of DTs
- Generalized Tonic-Clonic Seizures
- 40%-75% are isolated
- 3% with true Status Epilepticus
- Very short post-ictal period
- Worsened by neuroleptics
- Lorazepam reduces recurrent seizures from 24-3%
  (D'Onofrio NEJM 1999)
- No Role for Phenytoin in treatment/recurrence
- Less than 50% of seizures in Alcoholics

Delirium Tremens

- Usually occurs 48-96hrs after cessation
- AWS plus Disturbance of Consciousness or Change in cognition
- Can last up to 14 days
- Can be associated with benzodiazepiene resistance
  - >40mg diazepam to achieve MS control (Nelson 2003)

Pathophysiology



Moss Lancet 2006

Treatment- Which agents?

- IV hydration
  - In one study, dehydration was present in all AWS deaths (Moore NEJM 1939)
  - Main factor in declining mortality
- Thiamine to prevent Wernicke's
- Folate
- Low threshold for co-morbid conditions
  - Infection
  - Head trauma

What is standard outcome measure?

- Mortality is too low to be used for outcome
- Cost/number of doses required
- Duration of hospital stay
  - Very confounded as many subjects have other social/medical issues
- Many trials look at drugs looking for new indication
- Is less benzodiazepine a valid endpoint?

A bit more History… Kaim et al (Am J. Psych. 1969)

- 537 subjects with ETOH withdrawal randomized to Chlordiazepoxide, Chlorpromazine, hydroxyzine, thiamine and placebo.
  - Largest trial RCT in ETOH withdrawal
- Endpoint prevention of DTs, seizures

	Early Withdrawal	Delirium	Seizures
Chlordiazepoxide (103)	13.5%	1%	1%
Chlorpromazine (98)	25.5%	7%	12%
Hydroxyzine (103)	16.5%	4%	8%
Placebo (130)	20%	8%	7%
Thiamine (103)	23.3	4%	7%

Treatment-Benzodiazepines

- Mainstay of therapy
- Wide therapeutic index
- $GABA_A$ agonists
- No real difference between benzodiazepienes
- Diazepam (Valium) $T_{1/2}$=43hrs
  - Oral and IV-Rapid onset
  - Active metabolites allow for autotitration
  - All equally efficacious for symptoms
- Lorazepam (Ativan) (1:5 with diazepam) $T_{1/2}$=14hrs
  - No metabolites-preferred for cirrhosis
  - ? Seizures
- Chlordiazepoxide (Librium) $T_{1/2}$=10-12hrs
  - Oral Only
  - Similar to Lorazepam in RCT (Kumar 2009)

Treatment-Barbiturates

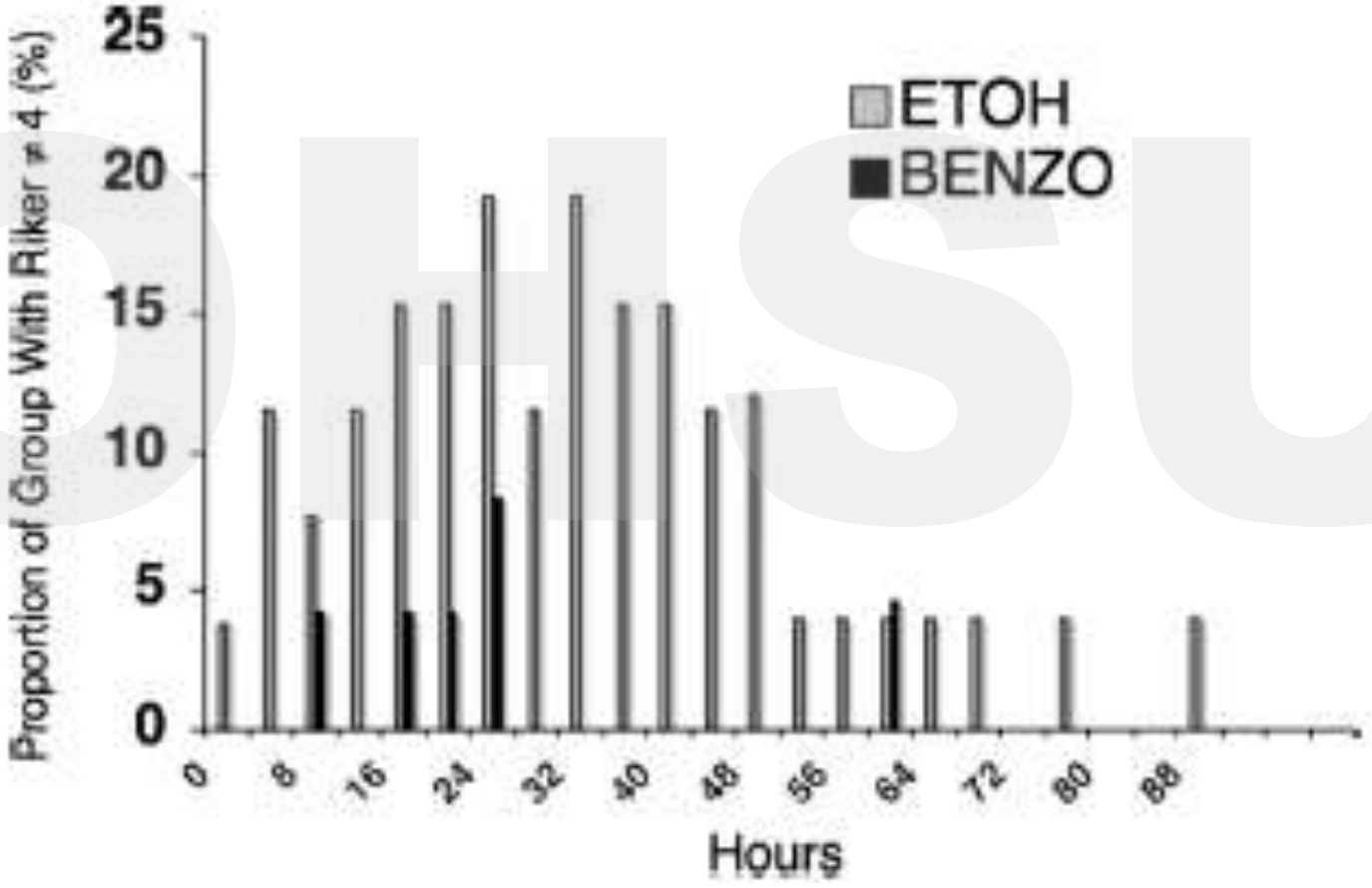
- Powerful $GABA_A$ agonists
  - Synergistic with benzodiazepines for GABA activation binding and activation (Delorey Anesth Analg 1993)
- May be mild Inhibitors of Stimulatory NMDA receptors (Patrenko Anest Analg 2004)
- Very effective in controlling symptoms
  - Superior to diazepam for “severe AWS” (Kramp Acta psychiat scand 1978)
  - Similar to Lorazepam and Diazepam (Hendy Ann Emer Med 2009, Hjermo Dan med Bull 2010)
- Narrower therapeutic index
- Best for synergy in difficult cases….

Ethanol

- #1 treatment of outpatient alcoholics
- 70% of US hospitals have ETOH on Formulary (Blondell JAMA 2003)
- Most studies titrate to Ethanol level-difficult
- No RCT for intravenous or oral ethanol of significant size for treatment
  - Failure rate of 33% for prophylaxis (Spies CCM 2002)
- Numerous reports of resistance to ETOH once DTs has begun
- Numerous adverse effects on general organ function and immune dysfunction
  - 1 month abstinence improves outcome in surgical patients (Tonnenson BMJ 1999)
  - Unclear if much different than benzos

ETOH vs. Diazepam for Prophylaxis

(Weinberg J.Trauma 2008)



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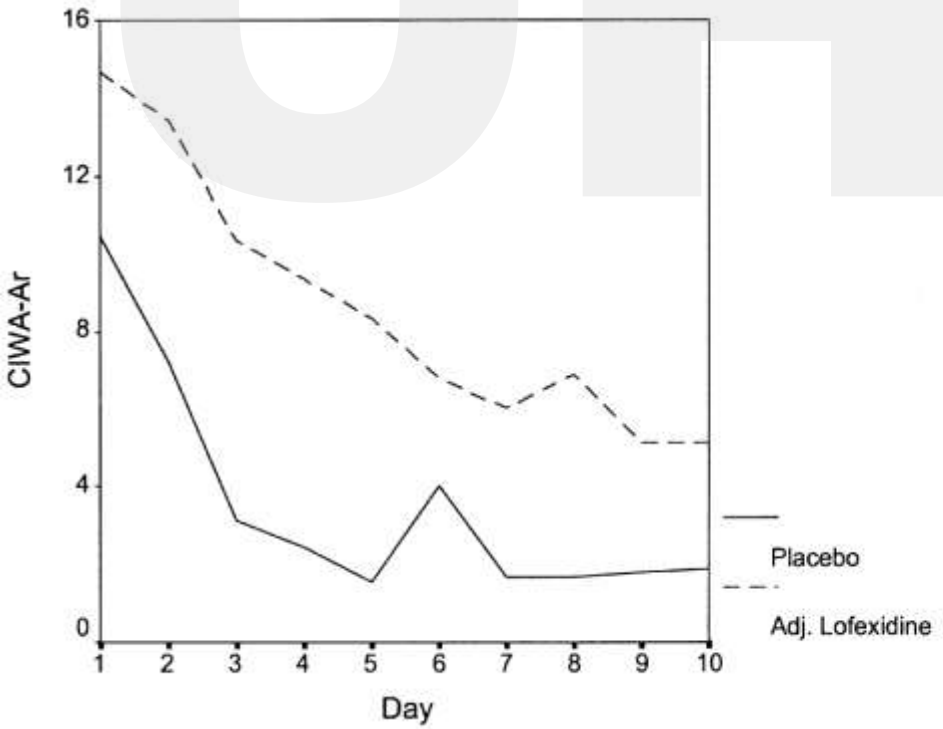
α-Hypertensive Agents

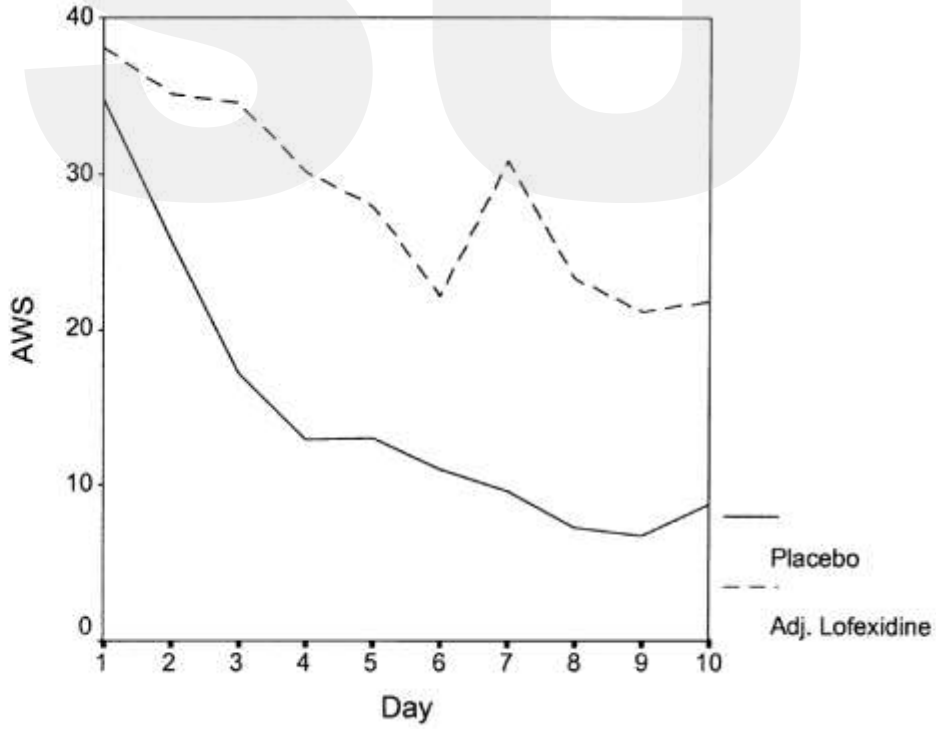
- Used to treat autonomic symptoms
  - Not a cause of death
  - May lead to under-treatment/recognition of delirium
- β-blockers
  - Improve overall autonomic tone (Kraus NEJM 1985)
  - Increased Delirium in one RCT (Worner 1985)
- Clonidine/Lofexidine
  - Similar to Chlordiazepoxide for BP control in mild withdrawal (Baumgartner Arch Int Med 1987)
  - No effect on non-autonomic signs of AWS (Adinoff Alcohol Clin. Exp res 1994, Robinson 1989)
- Dexamedatomidine-

Effects of Lofexidine on AWS

(Keaney Alcohol Alcoholism 2001)

- Randomized placebo controlled trial of Lofexidine as adjunct to Chlorodiazepoxide
- Pts RX in symptom triggered fashion





Neuroleptics

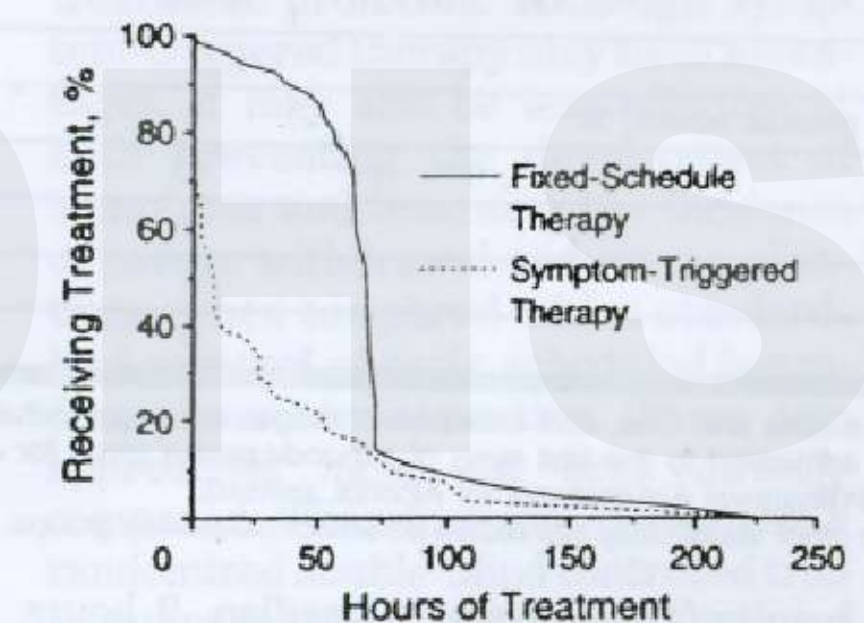
- Adequate in controlling symptoms
- Chlorpromazine increased seizures (Kaim 1967)
- Haloperidol increases seizures in rodents (Blum Clin Toxic 1976)
- Increased mortality with haloperidol vs. Chlormethiazole (6 vs. 0%; n=70/arm) and longer duration of delirium (96 vs. 70hrs.) (Athen Acta Psychitr. Scand. 1986)
- No randomized studies for use of Haloperidol as adjunct to BDA
- Should not be used in early AWS
  - If used, only with adequate BDA

Treatment-Propofol

- GABA activator
- NMDA inhibitor
- Can act synergistically with both barbiturates and benzodiazepine
- Easily titratable
- Narrow Therapeutic window
- Mostly case reports in benzodiazepine resistant withdrawal
- Maye associated with longer time on vent compared to high dose BDA (Wong Drug Alch Depend 2015)

Benzodiazepine administration

- Symptom triggered vs. standing (Saitz 1994)



- Symptom triggered with 5x less benzodiazepine
- In general Detox unit only 39% of Alcoholics required Rx (Daeppen Arch Int Med 2002)
- Based on rebolusing for CIWA≤10

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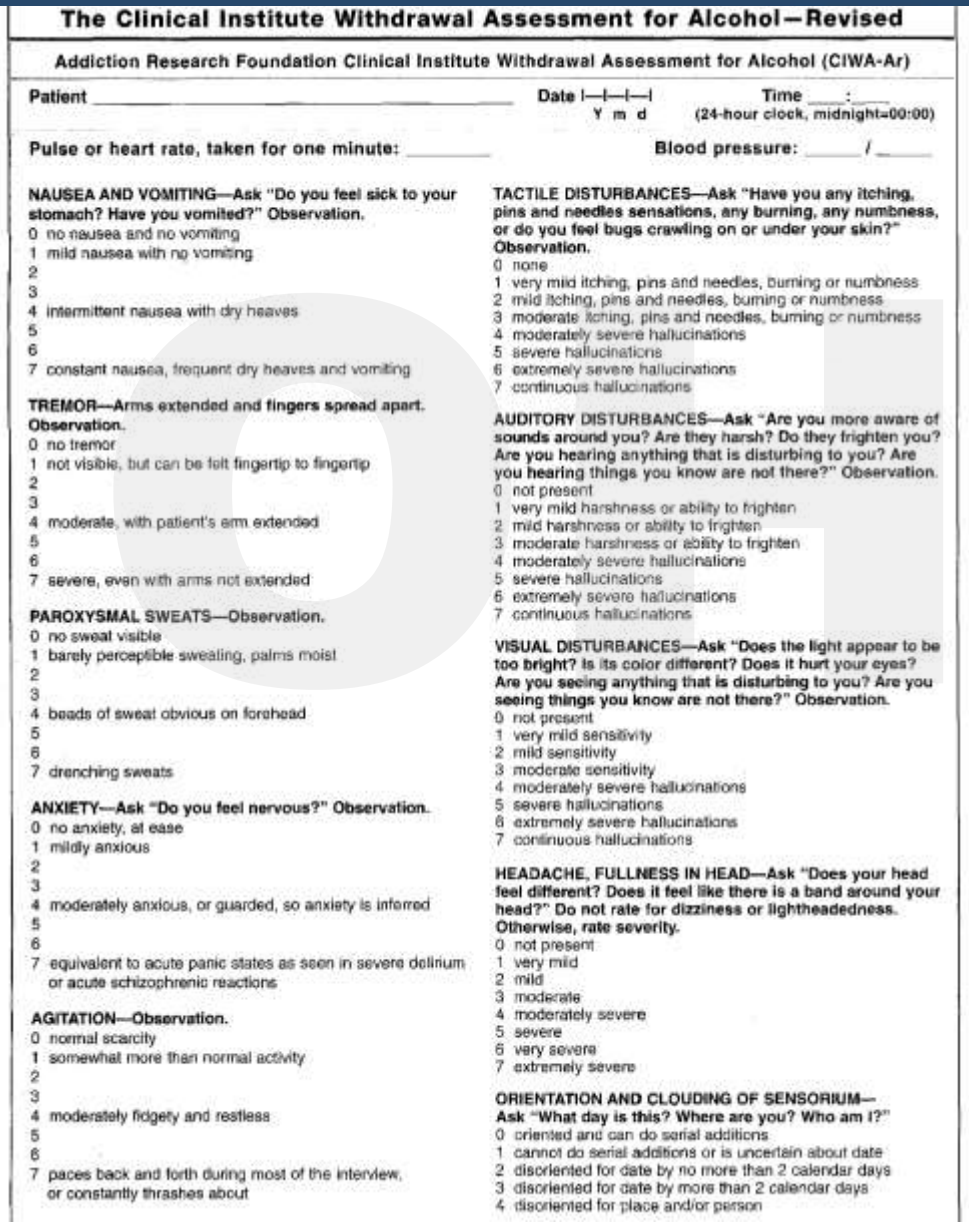
The CIWA-Ar



The Clinical Institute Withdrawal Assessment for Alcohol—Revised

Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

Patient _____ **Date** I—I—I—I—I—I (Y m d) **Time** ___:___ (24-hour clock, midnight=00:00)

Pulse or heart rate, taken for one minute: _____ **Blood pressure:** _____ / _____

NAUSEA AND VOMITING—Ask "Do you feel sick to your stomach? Have you vomited?" Observation.
0 no nausea and no vomiting
1 mild nausea with no vomiting
2
3
4 intermittent nausea with dry heaves
5
6
7 constant nausea, frequent dry heaves and vomiting

TREMOR—Arms extended and fingers spread apart. Observation.
0 no tremor
1 not visible, but can be felt fingertip to fingertip
2
3
4 moderate, with patient's arm extended
5
6
7 severe, even with arms not extended

PAROXYSMAL SWEATS—Observation.
0 no sweat visible
1 barely perceptible sweating, palms moist
2
3
4 beads of sweat obvious on forehead
5
6
7 drenching sweats

ANXIETY—Ask "Do you feel nervous?" Observation.
0 no anxiety, at ease
1 mildly anxious
2
3
4 moderately anxious, or guarded, so anxiety is inferred
5
6
7 equivalent to acute panic states as seen in severe delirium or acute schizophrenic reactions

AGITATION—Observation.
0 normal activity
1 somewhat more than normal activity
2
3
4 moderately fidgety and restless
5
6
7 paces back and forth during most of the interview, or constantly thrashes about

TACTILE DISTURBANCES—Ask "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling on or under your skin?" Observation.
0 none
1 very mild itching, pins and needles, burning or numbness
2 mild itching, pins and needles, burning or numbness
3 moderate itching, pins and needles, burning or numbness
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

AUDITORY DISTURBANCES—Ask "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation.
0 not present
1 very mild harshness or ability to frighten
2 mild harshness or ability to frighten
3 moderate harshness or ability to frighten
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

VISUAL DISTURBANCES—Ask "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation.
0 not present
1 very mild sensitivity
2 mild sensitivity
3 moderate sensitivity
4 moderately severe hallucinations
5 severe hallucinations
6 extremely severe hallucinations
7 continuous hallucinations

HEADACHE, FULLNESS IN HEAD—Ask "Does your head feel different? Does it feel like there is a band around your head?" Do not rate for dizziness or lightheadedness. Otherwise, rate severity.
0 not present
1 very mild
2 mild
3 moderate
4 moderately severe
5 severe
6 very severe
7 extremely severe

ORIENTATION AND CLOUDING OF SENSORIUM—Ask "What day is this? Where are you? Who am I?"
0 oriented and can do serial additions
1 cannot do serial additions or is uncertain about date
2 disoriented for date by no more than 2 calendar days
3 disoriented for date by more than 2 calendar days
4 disoriented for place and/or person

- **K=0.67 in one study unclear in real world (Wetterling 1994)**
- **CIWA>10-15 predicative of need for Inpt. Detox**
- **Used for triggering of meds**
- **Used but not validated in ICU**

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Inappropriate Use of CIWA (Hecksel 2008)

TABLE 2. **History of AD and the Incidence of Adverse Events During Symptom-Triggered Therapy**[a]

	Adverse events, No. (%) of patients	
History of AD	Yes	No
Yes (n=68)	10 (15)	58 (85)
No (n=56)	1 (2)	55 (98)

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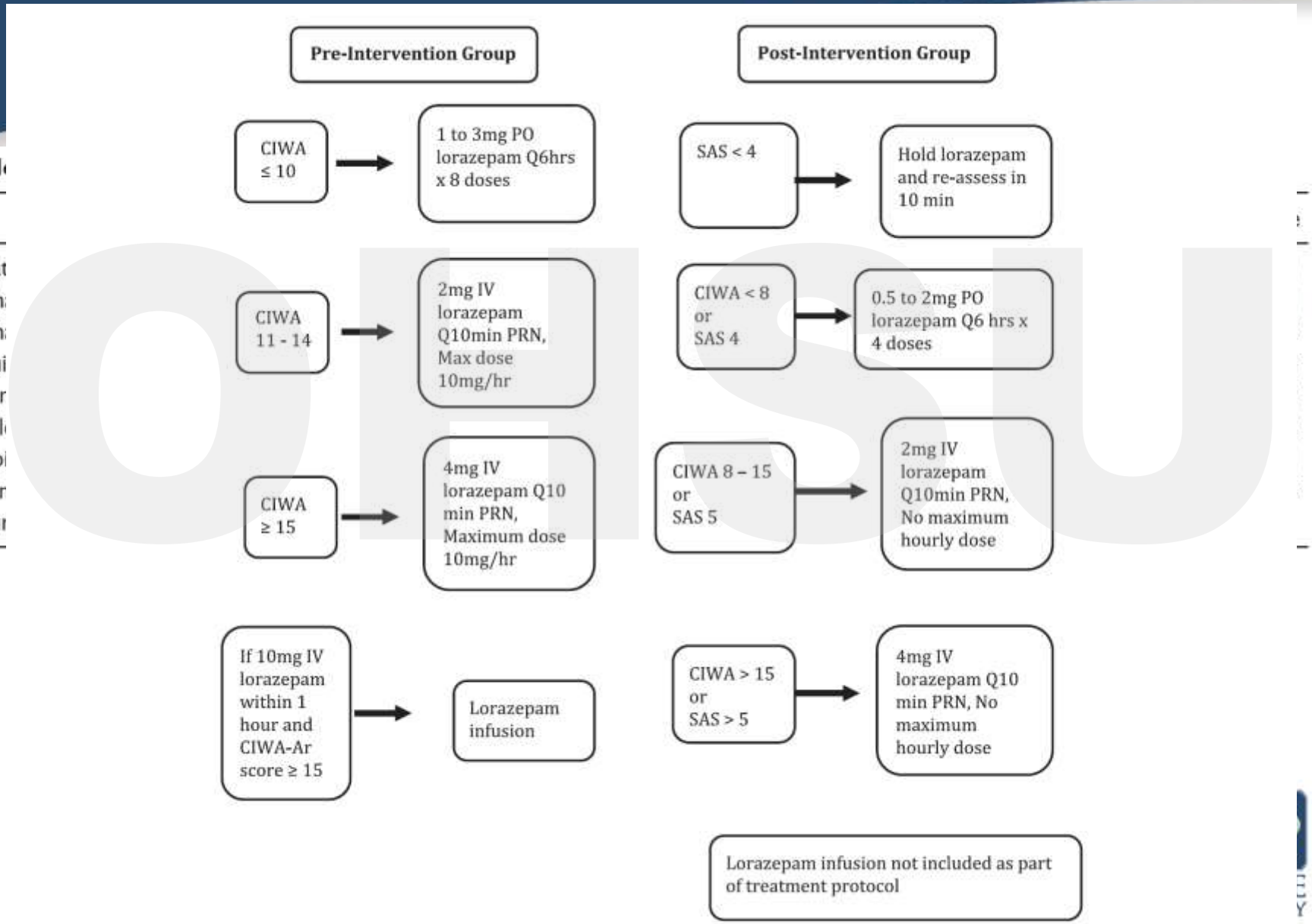
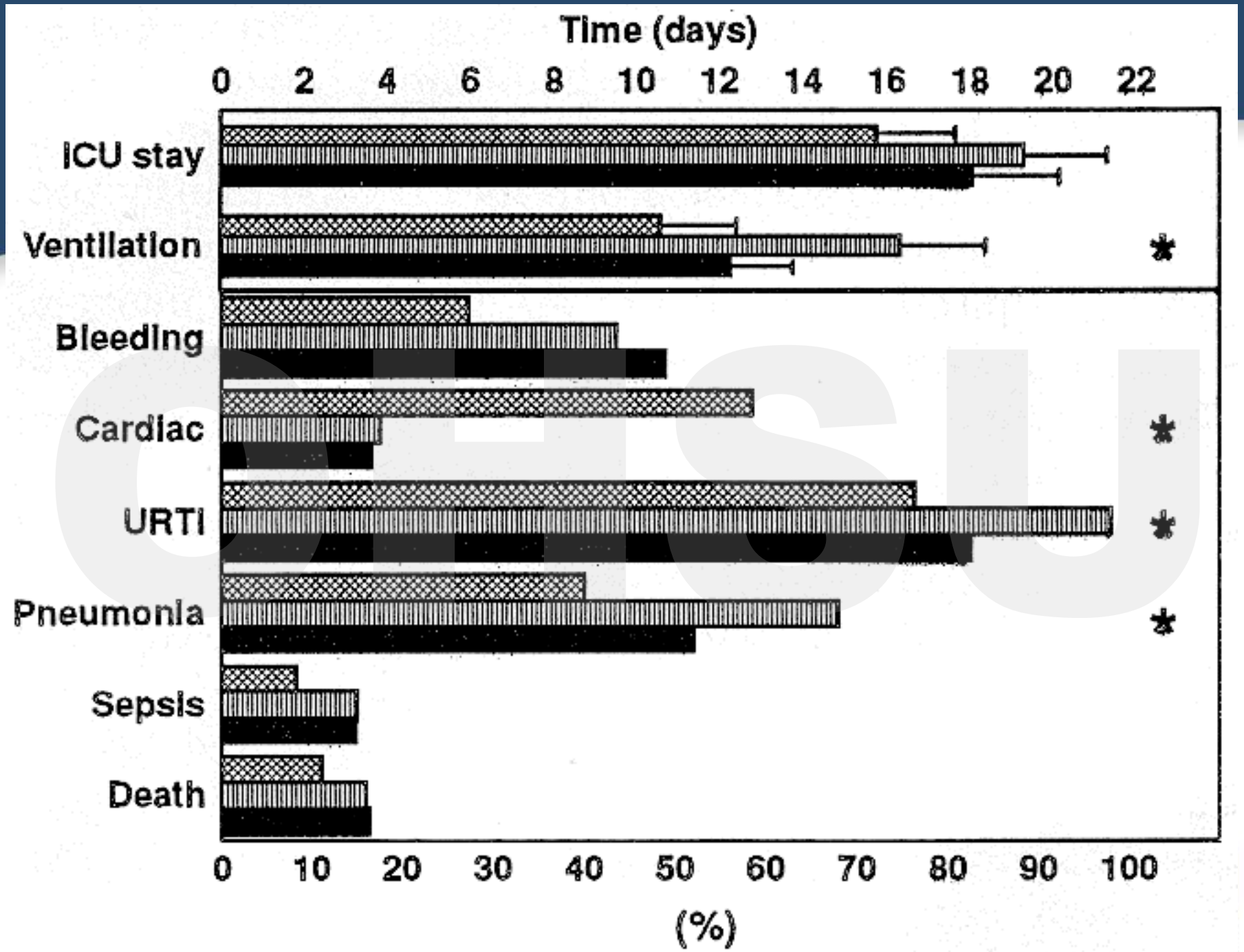
What About In ICU (Sen Ann Pharm 2016)

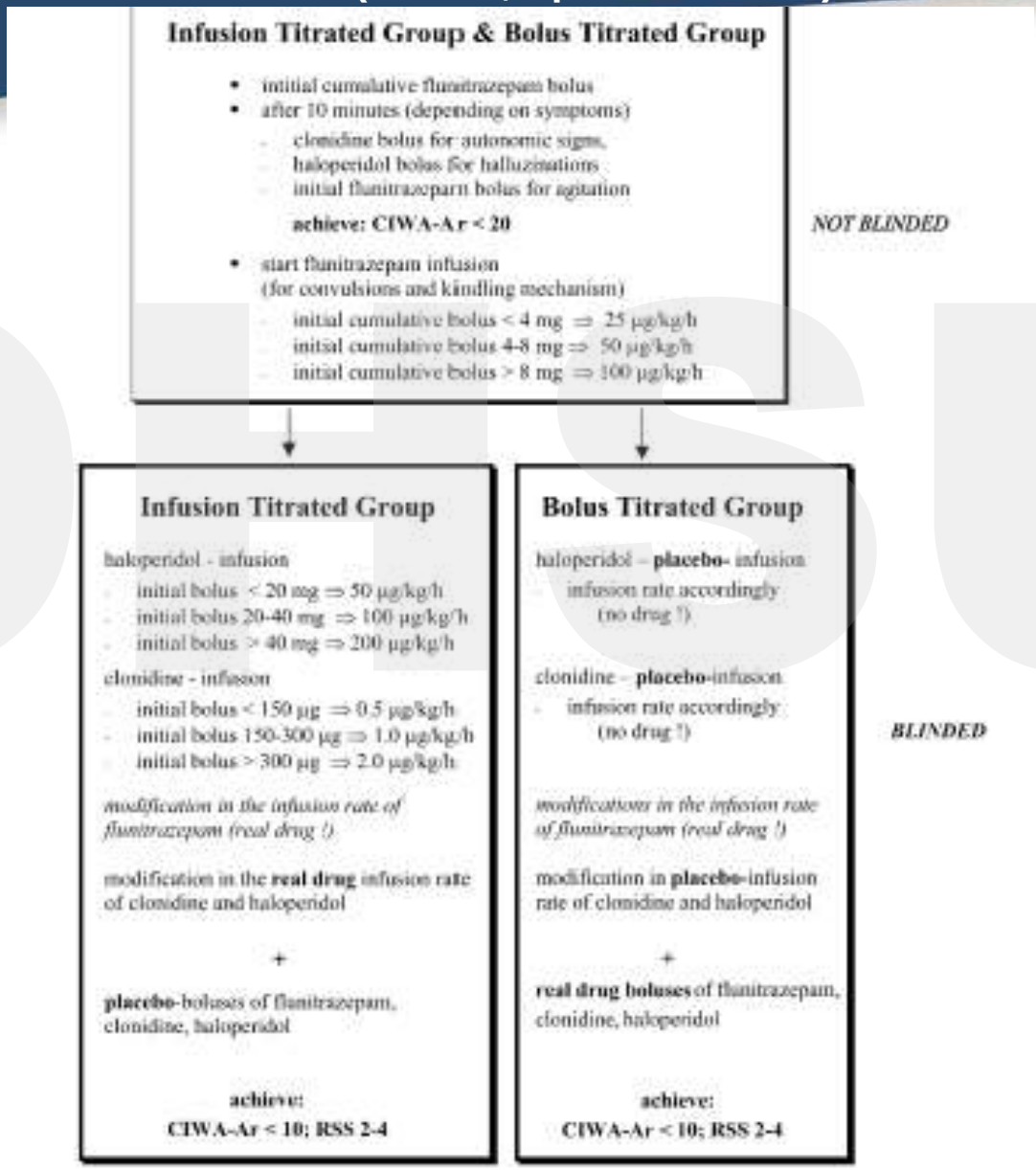


Comparison of 3 regiments for post-op ETOH withdrawal (Spies CCM 1996)

	Flunitrazepam/ Clonidine (n = 54)	Chlormethiazole/ Haloperidol (n = 50)	Flunitrazepam/ Haloperidol (n = 55)	*p* Value
TRISS	0.85 (0.03–1.00)[a]	0.83 (0.12–0.99)	0.84 (0.03–0.99)	.3757
ISS	21.5 (4–48)	25.5 (16–43)	21 (9–41)	.7097
RTS	6.05 (3.50–7.84)	6.26 (4.71–7.84)	5.40 (2.83–7.84)	.1010
Pao_2/Fio_2 (prior ICU admission)	395 (172–516)	412 (185–526)	397 (128–556)	.2623
Surgery (prior ICU admission)	45/54 (83%)	39/50 (78%)	42/55 (76%)	.2707
Blood transfusion (mL) (prior ICU admission)	2000 (0–16750)	2000 (0–7900)	2500 (0–12000)	.3998
APACHE II (on ICU admission)	25 (9–47)	28 (10–43)	24 (8–47)	.6780
MOF (on ICU admission)	6.5 (1–14)	7 (2–14)	6 (1–14)	.3239


Time (days)
0 2 4 6 8 10 12 14 16 18 20 22
ICU stay
Ventilation
*
Bleeding
Cardiac
*
URTI
*
Pneumonia
*
Sepsis
Death
0 10 20 30 40 50 60 70 80 90 100
(%)

Does method of administration matter in ICU? (Sellers, Spies ICM 2005)



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Does method of administration matter in ICU? (Sellers, Spies ICM 2005)

	BTG (n=23)	ITG (n=21)	p
Period until onset of AWS (days)	2 (2–4)	2 (2–4)	0.12
Maximal systolic blood pressure (mmHg)	198 (180–227)	180 (167–201)	≤0.01
Maximal heart rate (beats/min)	119 (108–131)	130 (112–145)	0.21
PaO_2/FIO_2, onset of AWS (mmHg)	328 (280–441)	341 (269–487)	0.51
Maximal RSS, during AWS therapy (days)	4 (3–6)	5 (4–6)	≤0.01
Duration of AWS (days)	2 (2–4)	6 (4–10)	≤0.01
Intubated patients following onset of AWS	15 (65%)	19 (90%)	0.05
Time until intubation after onset of AWS (days)	2 (1–2)	2 (1–2)	0.13
Duration of ventilation (days)	6 (3–8)	12 (5–20)	≤0.01
Flunitrazepam	23 (100%)	21 (100%)	
Initial bolus (mg)	3 (1–8)	2 (2–4)	0.19
Number of boluses, each adjustment	4 (1–11)	3 (2–4)	0.49
Infusion rate, max. (μg/kg per hour)	12.1 (0–26.7)	25.0 (17.5–87.4)	≤0.01
Total amount (mg)	69.7 (12.5–143.9)	162.0 (91.4–807.0)	≤0.01
Clonidine	13 (57%)	16 (76%)	0.17
Initial bolus (μg)	150 (150–300)	75 (37.5–150)	≤0.01
Number of boluses, each adjustment	4 (2–6)	2 (1–4)	≤0.01
Infusion rate, max. (μg/kg per hour)	0	5.5 (2.2–7.4)	≤0.01
Total amount (μg)	1,270 (1,050–4,768)	61,098 (7,188–147,384)	≤0.01
Haloperidol	13 (57%)	12 (57%)	0.97
Initial bolus (mg)	10 (15–70)	5 (3–70)	0.89
Number of boluses, each adjustment	6 (3–8)	2 (1–2)	≤0.01
Infusion rate, max. (μg/kg per hour)	0	412 (85–1310)	≤0.01
Total amount (mg)	180 (80–554)	1713 (270–3,288)	≤0.01
Propofol, rescue	8 (35%)	10 (48%)	0.39
Total number of boluses	34 (12–81)	53 (8–164)	0.01
Total amount (g)	6.10 (2.15–15.10)	8.95 (1.40–21.50)	0.03
Fentanyl, intubated			
Infusion rate, max. (mg/h)	0.3 (0.2–0.5)	0.3 (0.2–0.5)	0.81
Total amount (mg)	51 (12–64)	78 (23–110)	≤0.01[a]
Piritramide, extubated			
Total number of boluses	18 (6–41)	21 (11–36)	0.39
Dose of each bolus (mg)	5 (3–12)	5 (3–12)	0.92
Total amount (mg)	121 (41–395)	106 (39–371)	0.21

Strategy of Escalating Doses of BDA

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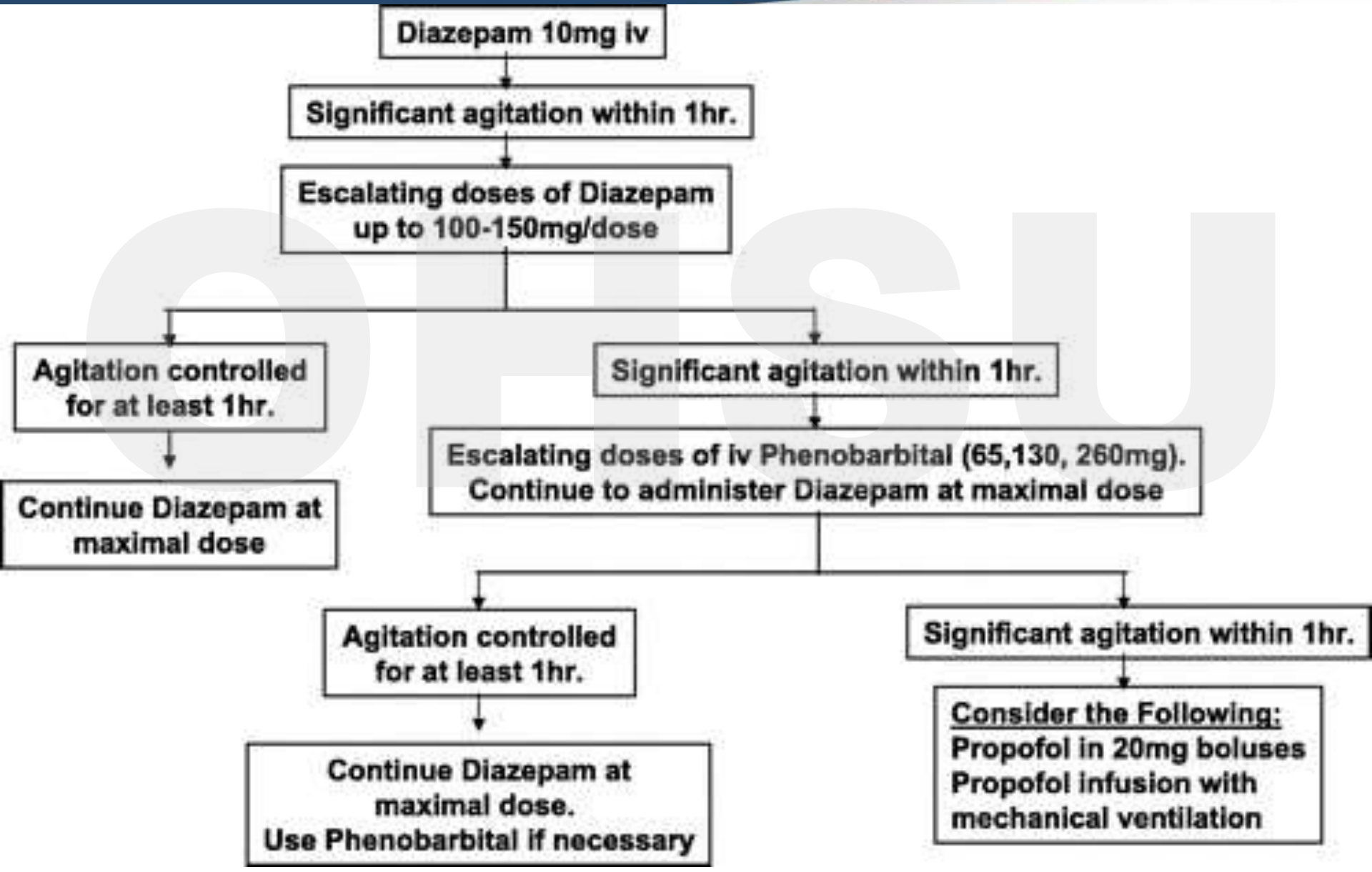
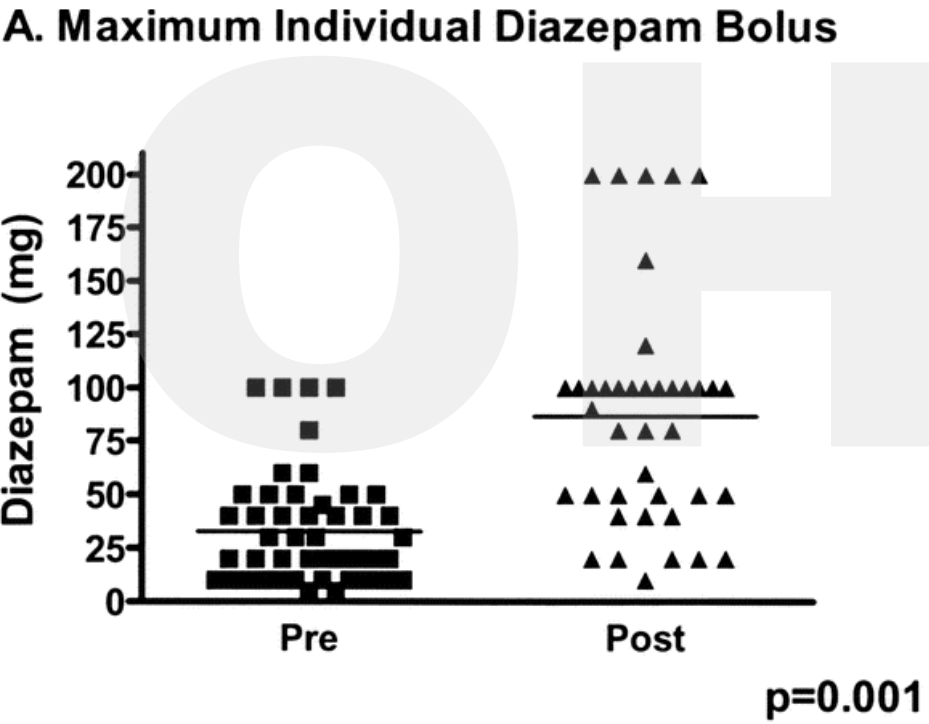
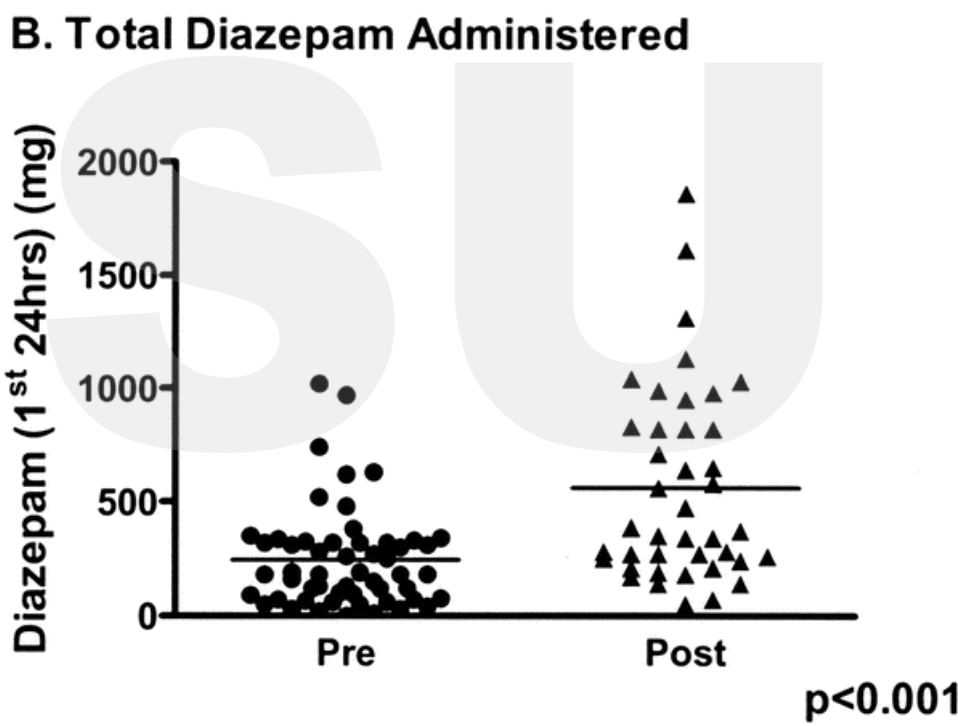


Treatment guidelines significantly alter benzodiazepine administration





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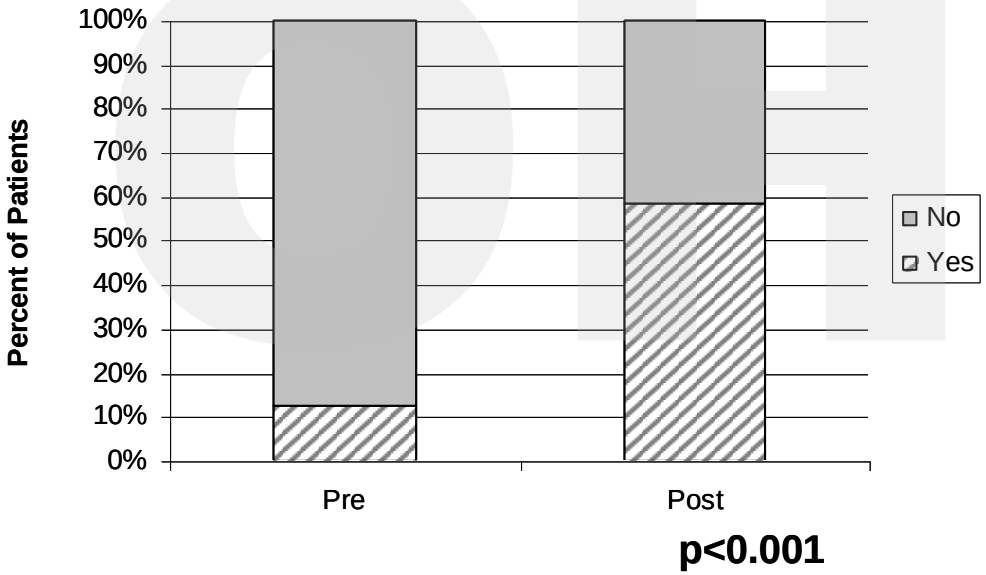
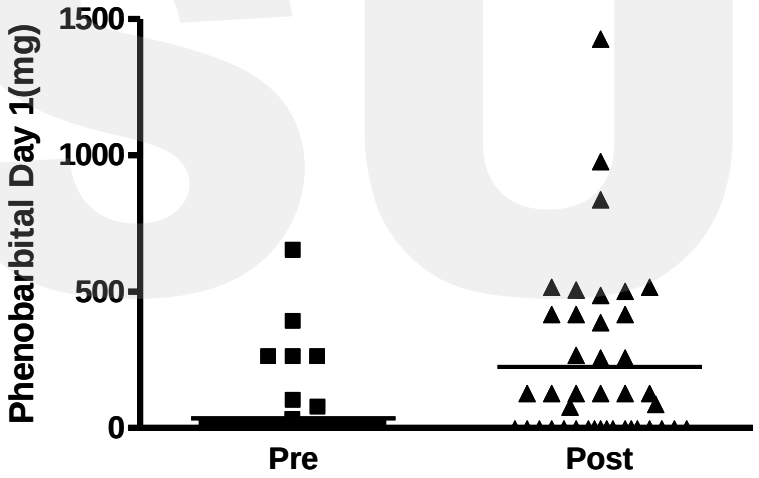
Treatment guidelines significantly increase barbiturate administration

A. % Receiving Phenobarbital



p<0.001

B. Total Amount of Phenobarbital



p<0.001

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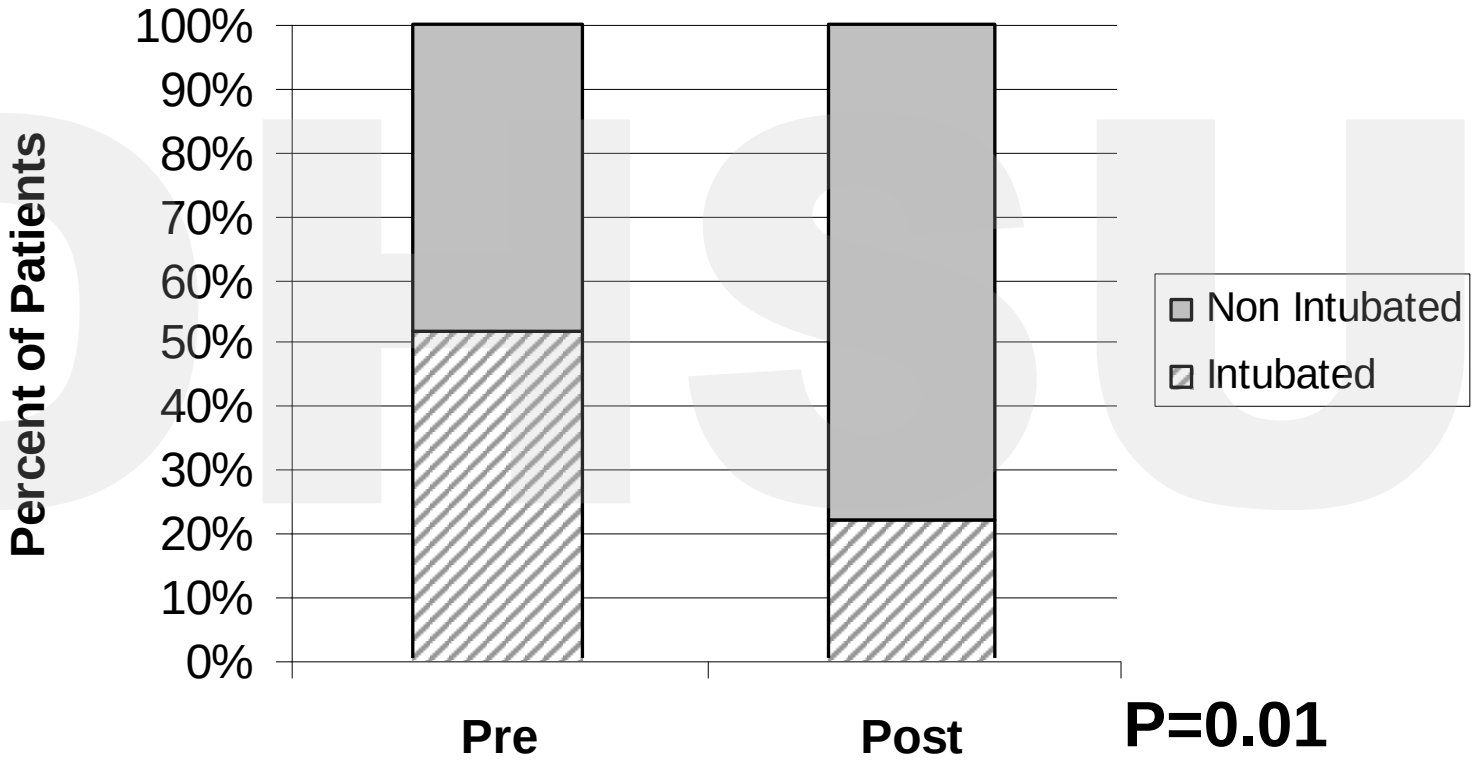
Treatment guidelines reduce need for mechanical ventilation



All but 1 subject post guideline intubated for mental status control- 1 due to oversedation)

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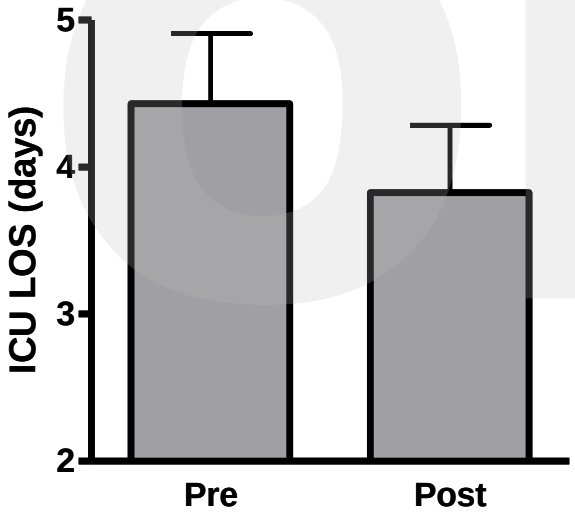
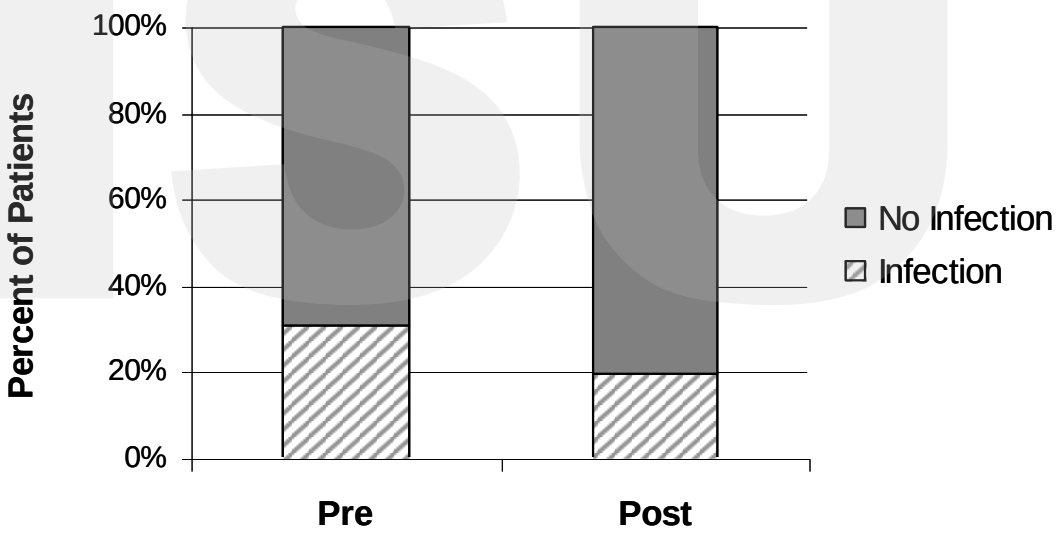
Treatment guidelines are associated with reduced ICU LOS and nosocomial infections

A. ICU LOS



B. Nosocomial Infections



 # needed/group approximately 100 to detect significant difference

Dexamedatomidine for Benzo resistant

- Bas nc with
  - S
- Mec
  - 2
  - 1
  - 6
  - 2
- No ler CCM

Table 1 Analysis Comparing Pre- and Post-Dexmedetomidine Data

Endpoint	Sample size (n) for endpoint	24 h before dex	First 24 h of dex therapy	Decrease in values following dex initiation (percent decrease)	*p* value	95% Confidence interval for decrease seen after dex initiation
Average alcohol withdrawal scoring	11	9.0	7.1	1.9 (21.1%)	0.015	0.44–3.36 (4.9–37.3%)
Average benzodiazepines received (mg)	17	52.7	20.3	32.4 (61.5%)	<0.001	16.7–48.1 (31.7–91.3%)
Average haloperidol received (mg)	17	12	6.4	5.6 (46.7%)	0.052	0.03–11.23 (−0.36–93.6%)
Average HR	17	102.8	79.3	23.4 (22.8%)	<0.001	18.4–28.4 (17.9–27.6%)
Average SBP	17	140.2	126.7	13.5 (9.6%)	0.002	5.32–21.68 (3.8–15.4%)
Hours with HR > 100	16	13.3	2.3	10.9 (82%)	<0.001	7.4–14.4 (55.6–108.3%)
Hours with SBP >140	16	11	6.3	4.7 (42.3%)	0.02	0.8–8.6 (3.8–15.4%)
Hours with HR <60	16	0	2	−2	0.055	4.05–0.05
Hours with SBP <90	16	0	0.9	−0.9	0.079	1.89–0.09

Phenobarbital…Its a Coming

- 6 studies in last 5 years documenting safety and efficacy
- Used in symptom triggered and as loading dose (Rosenson Acad Emer Med 2013)

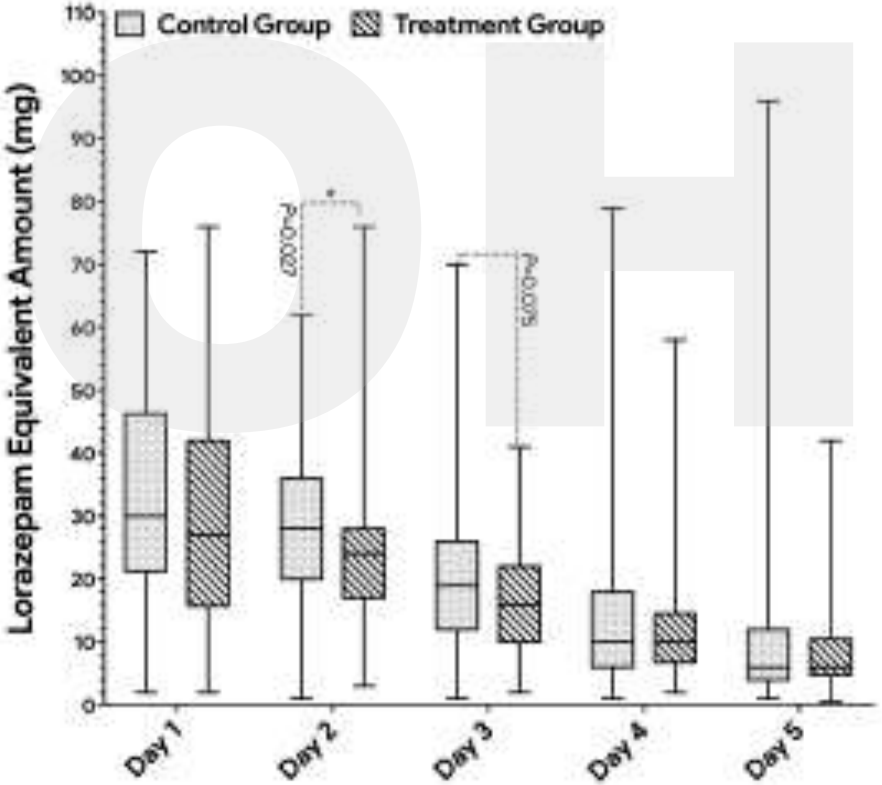
Table 2. Clinical Outcomes

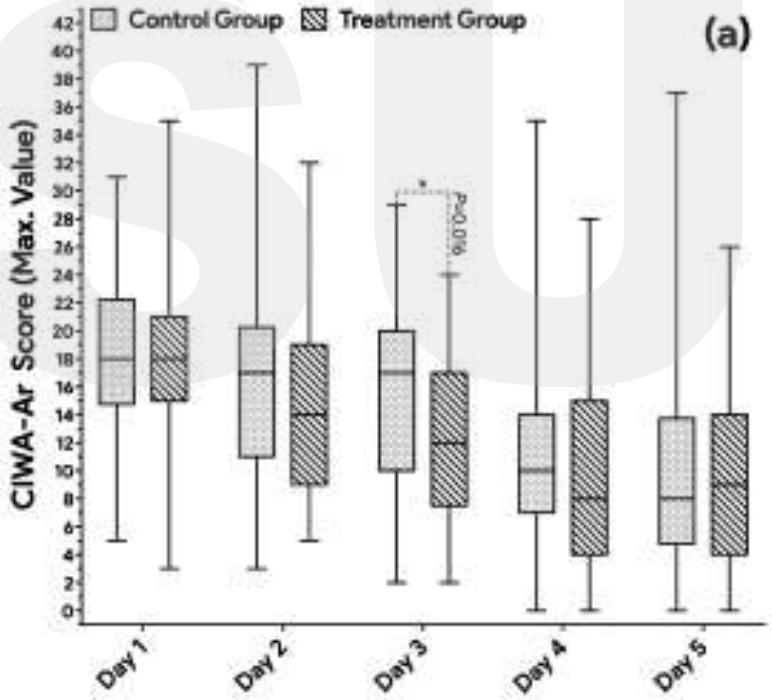
Clinical Outcome*	Phenobarbital (n = 51)	Placebo (n = 51)	Difference (95% C
ICU admission: n (%)	4 (8)	13 (25)	17 (4–32)
TCU admission, number: n (%)	23 (45)	20 (39)	−6 (−25–13)
Floor admission: n (%)	24 (47)	18 (35)	−12 (−31–7)
Maximum AWCA score: median (IQR)	8 (5–10)	10 (5–14)	2 (−0.2–3)
Continuous 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)

Gabapentin

- Potentiates GABA activity but not direct GABA binder
- Very effective (1800mg/d) reducing ETOH dependence (Mason Jama Int Med 2014)
- Total 5 studies performed in AWS
  - Almost all patients mild or outpatient
  - No real benefit over BDA
  - Some studies with reduced drinking (in outpatient)
  - 6% incidence of seziures in treatment arms
  - Worse symptoms in DTs or severe AWS
- Should not be used as sole agent, in patients with history of seizures or maybe not DTs

High Dose Gabapentin (Levine et al 2019)





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Take Home Points

- In ICU, use RASS to determine dosing
- If your first dose fails (<1hr control) increase it (same as diuretic dosing)
- Gabapentin is a useful adjunct
- Vital signs ARE NOT part of dosing decision!
- AWS is diagnosis of exclusion. Not all drinkers get it
- Goal is not to sleep, but just try not to hurt you or themselves

Conclusions

- Be aware of ETOH withdrawal in ICU- it is more common than you think
- Symptom triggered therapy
- Maximal dose of benzodiazepine is determined by clinical effect
- Utility of Clonidine and Haloperidol still unclear
- Role for empiric prophylaxis unclear
- Barbiturates and Propofol may be used for synergy in benzodiazepine resistance
- Little data supports added benefit to Dexamedatomidine
- Strategies aimed at reducing intubation may improve outcomes

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It’s not that drinking that kills you, it’s the stopping!