Alcohol Withdrawal Syndrome
Treatment options beyond benzodiazepines

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With respect to this presentation, there has been no relevant (direct or indirect) financial relationship between Dr. Maldonado (and/or spouse) and any for-profit company in the past 10 years which could be considered a conflict of interest.
Hospital Setting

- In a study performed at a major university hospital, 30% of patients admitted to the medical units (for reasons other than alcohol abuse or withdrawal) experienced alcohol withdrawal symptoms requiring pharmacologic treatment (Maldonado 2000).

- According to a nationwide survey of the Veterans Affairs system, 42% of all veteran inpatients required medications to aid detoxification from alcohol (Tracey 2004).

- Of patients presenting for alcohol detoxification up to 73% will develop significant symptoms of alcohol withdrawal requiring pharmacologic intervention (Wartenberg 1990, Saitz 1997).

- Almost half of all trauma beds are occupied by patients who were injured while under the influence of alcohol (Herve et al 1986; Gentilello et al 1995; Soderstrom et al 1992; Spies et al 1996).

* All based in USA data
Hospital Setting

- Chronic alcohol misuse is more common in surgical patients (e.g., up to 43% in EENT) than in psychiatric (30%) or neurological (19%) patients. ¹

- In addition to the life-threatening complications of alcohol withdrawal syndrome (AWS):
  - In General Medicine: the rate of morbidity and mortality due to infections, cardiopulmonary insufficiency, or bleeding disorders is 2 to 4 times greater in chronic alcoholics. ²-⁷
  - In Surgical Services: ⁸-¹²
    - 2 – 3X the morbidity of pts who drink <2/d
      - More 2ry surgeries
      - 50% longer hospital stay
      - Pooper 3-month outcome
      - Complications: infections, bleeding problems, cardiopulmonary insufficiency.

Pharmacology of Ethanol

- Complete absorption: 2 – 6 hrs
- Most foods retard absorption
- 90 – 98% is heptically metabolized via oxidation at a relatively slow rate following zero-order kinetics (i.e., independent of time and concentration)
- Average rate of metabolism:
  - About 20 mg/dl/hr or
  - Roughly 1 oz of hard liquor/1.5 hrs
  - A rule of thumb is that the average rate of fall is 0.02 g% per hour which coincidentally is also the level to which the blood alcohol rises after a single standard (10 g) drink.
  - ~2% escapes oxidation and is excreted via kidneys and lungs
- Prolonged use of alcohol is associated with the accumulation of protein and fat in the liver, leading to various stages of hepatic disease culminating in cirrhosis
Effects of Acute Ethanol in Non-Habituated Individuals

- Ataxia, prolonged reaction time, poor coordination, mental impairment *
- Confusion and ↓ consciousness
- Stupor, hypothermia, amnesia, stage I anesthesia
- Anesthesia, unconsciousness
- Alcohol coma
- Death *

Blood Alcohol Concentration (mg/100ml)

- 0.05 = 50mg/100dl (mild coordination problems; changes in mood, personality and behavior)
- 0.1 = 100mg/100dl
- 0.2 = 200mg/100dl
- 0.3 = 300mg/100dl
- 0.4 = 400mg/100dl
- 0.5 = 500mg/100dl
- 0.6 = 600mg/100dl

0.08 = 80mg/100dl (Legal driving limit in most states)
Alcohol Withdrawal Syndromes

- Tremors, irritability & insomnia
- Major Withdrawal (DT's)
- Minor Withdrawal
- Hallucinosis
- Seizures
- Confusion

Days

Symptom Intensity

Maldonado et al, 2009
Alcohol Withdrawal Treatment

Alcohol Replacement

**Drawbacks:**

- There is no scientific evidence demonstrating the utility of alcohol use in the management of alcohol withdrawal.
  - ↑ caloric content, lack of proteins and nutrients
  - Unfavorable TD/ED ratio. Difficult to titrate
  - Short T1/2
  - Perpetuates medical problems
  - Gastritis if given PO
  - Poor clinical utility
  - Only delays ultimate goal

- IV ETOH vs IV-Benzodiazepine studies have demonstrated no superior prophylactic effect; in fact, in a SICU study, more patients failed to be under adequate control in the IV-ETOH group

- There is little evidence from controlled studies to support this practice over standard treatments, and there are concerns regarding the efficacy, pharmacokinetic profile and narrow therapeutic index of ethanol, particularly in critically ill patients.

- In order to achieve adequate symptom control, IV ethanol had to be infused (for IV ethanol) or alcoholic beverages given (for PO alcohol consumption) to achieve a BAL = 0.08 = 80mg/100d [which is equal to legal intoxication levels in the USA].

- There are no adequate titration protocols.

*(Weinberg et al, 2008)*

*(Hodges & Mazur 2004)*

*(Dissanaike et all, 2006)*
Alcohol Withdrawal Treatment
Barbiturates

- Good cross-coverage to the CNS-D Rx.
- Effective in decreasing the incidence and rate of tremors and seizures in AWS.
- Long T1/2, provides good self-taper
- Are available PO, IM, or IV

- Drawbacks:
  - Unfavorable TD/ED ratio
  - Compared with long acting BZD, are no better, but do have more side effects
## Medications Commonly Used for Antianxiety/Hypnotic/Sedative Purposes

<table>
<thead>
<tr>
<th>Anxiolytics Generic Name</th>
<th>Trade Name</th>
<th>Class</th>
<th>Equi-Pot.</th>
<th>u-daily dose (mg)</th>
<th>Onset</th>
<th>T1/2</th>
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<tbody>
<tr>
<td>alprazolam</td>
<td>Xanax*</td>
<td>bzdp</td>
<td></td>
<td>0.75 – 4</td>
<td>R</td>
<td>12 – 15*</td>
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<tr>
<td>clonazepam</td>
<td>Klonopin</td>
<td>bzdp</td>
<td>0.5</td>
<td>0.25 – 4</td>
<td>I</td>
<td>18 – 50</td>
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<td>lorazepam</td>
<td>Ativan*</td>
<td>bzdp</td>
<td>1.0</td>
<td>0.5 – 6</td>
<td>I</td>
<td>8 – 20*</td>
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<td>midazolam</td>
<td>Versed</td>
<td>bzdp</td>
<td>2.5</td>
<td>N/A</td>
<td>R</td>
<td>2 – 4</td>
</tr>
<tr>
<td>diazepam</td>
<td>Valium</td>
<td>bzdp</td>
<td>5.0</td>
<td>2 – 40</td>
<td>R</td>
<td>30 – 100</td>
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<td>clorazepate</td>
<td>Tranxene</td>
<td>bzdp</td>
<td>7.5</td>
<td>7.5 – 60</td>
<td>R</td>
<td>50 – 100</td>
</tr>
<tr>
<td>chlordiazepoxide</td>
<td>Librium</td>
<td>bzdp</td>
<td>10</td>
<td>10 – 100</td>
<td>I</td>
<td>30 – 100</td>
</tr>
<tr>
<td>prazepam</td>
<td>Centrax</td>
<td>bzdp</td>
<td>10</td>
<td>10 – 60</td>
<td>S</td>
<td>50 – 100</td>
</tr>
<tr>
<td>oxazepam</td>
<td>Serax*</td>
<td>bzdp</td>
<td>15</td>
<td>15 – 120</td>
<td>S</td>
<td>5 – 15*</td>
</tr>
</tbody>
</table>

*= has no active metabolites. I = intermediate; R = rapid. U-dose = [ ] = usual dose. ‡= metabolized by glucuronidation (usually unaffected by hepatic failure); all other agents require oxidative metabolism. ≈= good SL absorption.

Jose R. Maldonado, MD 1997, 1999
Stanford University Study
“Prospective Comparison of Lorazepam versus Diazepam in the Treatment of Alcohol Withdrawal”

• **Design:** Prospective, randomized, case-control study @ SHC & PAVA

• **Loading method**
  – Requires the use of a long acting agent (e.g., diazepam, chlordiazepoxide)
  – Given every hour until sedation is achieved or significant improvement on the withdrawal scale score (e.g. CIWA-Ar)
  – Postulate that T½ will allow for Rx self-tapering, thus easier administration and avoidance of under-sedation.
  – Critics remark on the possibility of over-sedation, leading to possible respiratory depression and prolonged hospitalizations.

• **Symptom-triggered approach**
  – Promotes the use of short acting agents (e.g., lorazepam)
  – Administered based on threshold of withdrawal scale score
  – Postulate that avoidance of over-sedation may lead to faster resolution of the symptoms and earlier discharge from the hospital
  – Critics highlight possible “break-through” withdrawal, need for constant administration, development of benzodiazepine dependence.

*Maldonado et al, Gen Hosp Psychiatry. [Epub ahead of print]*
### Results

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<tr>
<th></th>
<th>Lorazepam</th>
<th>Diazepam</th>
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<tbody>
<tr>
<td>Total BZD Usage,</td>
<td>92.396</td>
<td>103.75</td>
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<tr>
<td>in diazepam</td>
<td>SD 103.47</td>
<td>SD 71.49</td>
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<tr>
<td>equivalents (mgs)</td>
<td>(p &gt;.05)</td>
<td>(p &gt;.05)</td>
</tr>
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<td>CIWA-Ar, Mean Rate</td>
<td>-3.62</td>
<td>-4.56</td>
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<tr>
<td>of Change (p &gt;.05)</td>
<td>SD 4.48</td>
<td>SD 3.41</td>
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<tr>
<td>Systolic B P, Mean</td>
<td>-2.73</td>
<td>-2.35</td>
</tr>
<tr>
<td>Rate of Change</td>
<td>SD 5.27</td>
<td>SD 6.28</td>
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<tr>
<td>(p &gt;.05)</td>
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</tbody>
</table>

Maldonado et al, Gen Hosp Psychiatry. [Epub ahead of print]
Why are BZDPs not always the Best?

- **10/1**: Pt involved on a fight - blow to L eye - admitted to Dominican Hosp @ 1500; reported LOC.
  - No record of BAL/Utox
  - HR 110-116; BP 138-146/88-92
  - Hx BAD.

- **10/1 @ 2100** transferred to SHC; no BAL on adm.

- **10/2 @ 0300** BAL=71.4mg/100dl; CAGE 4/4.
<table>
<thead>
<tr>
<th>Day</th>
<th>BAL</th>
<th>HR</th>
<th>BP</th>
<th>O2 sat</th>
<th>MSE</th>
<th>BZDP</th>
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</thead>
<tbody>
<tr>
<td>10/1</td>
<td></td>
<td>70-80s</td>
<td>139-158 /68-77</td>
<td></td>
<td></td>
<td>1mg-LOR</td>
</tr>
<tr>
<td>10/2</td>
<td>71.4mg /100dl</td>
<td>101-1 43</td>
<td>130-150 /80-90s</td>
<td></td>
<td>Restraints placed after became verbally aggressive and took a swing at a nurse</td>
<td>14mg-LOR 30mg-DIA</td>
</tr>
<tr>
<td>10/3</td>
<td></td>
<td>107-1 51</td>
<td>127-169 /82-91</td>
<td>88% on 4L</td>
<td>Broke through his restraints and tore his Posey- due to desaturation had to receive Flumezanil</td>
<td>24mg-LOR 30mg-DIA</td>
</tr>
<tr>
<td>10/4</td>
<td></td>
<td>110-1 30</td>
<td>131-145 /80-90s</td>
<td></td>
<td>Started on clonidine 0.2mg TDS, but d/cd within hrs p Psych consult. ativan 2mg IV prn for HR&gt;100, SBP&gt;160, DBP&gt;100, tremors, chills hold for sedation (note he was already sedated)</td>
<td>24mg-LOR 30mg-DIA</td>
</tr>
<tr>
<td>10/5</td>
<td>108-1 54</td>
<td>123-164 /73-95</td>
<td></td>
<td>C/L: 0.4mg clonidine patch, 0.5mg clonidine PO that day, VPA 500, 1000, decrease quetiapine 1000 to 500, ativan CIWA &gt;15</td>
<td>6mg-LOR 0-DIA</td>
<td></td>
</tr>
<tr>
<td>10/6</td>
<td></td>
<td>81-13 0</td>
<td>110/65-1 49/82</td>
<td></td>
<td>10/06/11 increased VPA to 2g. changed CIWA trigger to 20.</td>
<td>0</td>
</tr>
<tr>
<td>10/7</td>
<td></td>
<td>85-13 0</td>
<td>129-142 /74-92</td>
<td></td>
<td>10/07/11 we recommended stopping quetiapine completely and adding haldol 0.5mg BID, 2mg qhs and 2mg q8 h prn extreme agitation (only received once)</td>
<td>0</td>
</tr>
<tr>
<td>10/8</td>
<td></td>
<td>81-95</td>
<td>120-10s/70s</td>
<td></td>
<td>10/08/11 out of restraints (placed 10/02/11). no ativan since 10/5/11. HR down to the 80s. sitting in a chair</td>
<td>0</td>
</tr>
<tr>
<td>10/9</td>
<td></td>
<td>76-83</td>
<td>116/66-1 35/73</td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>
Alcohol Withdrawal Treatment

Alternative to Benzodiazepines

- Benzodiazepines represent the standard of care for the treatment of AWS and Tx prevention of alcohol withdrawal seizures and delirium tremens (Mayo-Smith, 1997)
- Potential problems with the use of BZD:
  
  I. BZD have abuse liability (Ciraulo et al., 1998). This is problematic in an outpatient setting or when trying to discharge home a patient on moderate or high doses.
  
  II. Concurrent alcohol/benzodiazepine use: 29 – 76% (Busto et al 1991; Ciraulo et al 1988)
  
  III. BZD blunt cognition which might hamper early attempts at rehabilitation counseling.
      - New evidence suggests that BZDP use may be associated with an increased risk of dementia (de Gage et al BMJ 2012).
  
  IV. BZD have significant interactions with alcohol, opioids, and other CNS-depressant agents. If taken together, there can be additive respiratory depression and cognitive impairment (Denaut et al 1974; Gross et al 1983).
  
  V. There are preclinical and clinical studies suggesting that BZD use may increase craving, early relapse to alcohol use, and increased alcohol consumption (Longo et al 2002; Malcolm et al., 2002; Poulos and Zack, 2004).
  
  V. Increased risk of developing BDZP-induced delirium; mostly due to it’s a-chol activity.

The probability of transitioning to delirium increased with the dose of lorazepam administered in the previous 24 h. This incremental risk was large at low doses and plateaued at around 20 mg/day. 

Pandharipande et al 2006
Results: Patient outcomes (e.g., length of stay and the incidence of delirium) improved for those patients who received benzodiazepines within the range of the pathway guidelines.

Repper, Stern et al, Psychosomatics, 2008
The “neurotransmitter hypothesis” suggests that changes in neurotransmitter concentration or receptor sensitivity (due to decreased oxidative metabolism in the brain causing cerebral dysfunction) may underlie the different symptoms and clinical presentations of delirium:

- Reduced availability of:
  - acetylcholine (↓ Ach)

- Excess release of:
  - dopamine (↑ DA)
  - norepinephrine (↑ NE)
  - glutamate (↑ GLU)

- Both decreased and increased activity in:
  - serotonin (↓↑ 5HT)
  - histamine (↓↑ H1&2)
  - gamma-aminobutyric acid (↓↑ GABA)
**A Basic Pathoetiological Model of Delirium**

Maldonado, Crit Care Clinic, 2008;24:789-856

- **Critical Illness**
  - $\downarrow O_2$ supply
  - $\uparrow O_2$ demand
  - $\downarrow O_2$ availability to brain tissue
  - ATP-ase pump failure
  - Na+ influx
  - K+ outflux
  - Ca+ influx
  - GLU release
  - NT release
  - Anoxic depolarization
  - ↑ tyrosine hydroxylase
    - + uncouples oxidative phosphorylation in brain mitochondria
  - DA production
    - + activation of intraneuronal catabolic enzymes
    - $\downarrow$ breakdown in ATP dependent transporters ($\downarrow$ NT reuptake)
  - ATP production
    - $\downarrow$ activity of $O_2$-dependent COMT
  - $\downarrow$ NAD:NADH ratio

- Cell swelling
  - i.e., hypoxia
  - i.e., hyperthermia: for every $1^\circ$C fever $\uparrow$ VO2 by 13%

- Cell swelling
  - ↑ cytotoxic quinones
    - (Graham '78)
  - ↑ NE
  - ↑ 5-HT$^3$

- NH4+
  - Activation of NMDA-receptors
    - (Felipo et al '98)

- EEG*
  - (Bauer '82; Koponen '89; Romano & Engel '44; Trzepacz '92)
  - (Carmen & Wyatt '77)
  - (Balestrino '95)
  - (Hall '92)

- $\uparrow$ DA activity
  - $O_2$- dependent COMT
    - (Gibson '81)
  - (Globus '88)

- $\downarrow$ cytotoxic quinones
  - (Graham '78)
# Theorized Neurochemical Mechanisms Associated With Conditions Leading To Delirium

*Modified from Maldonado 2008, Critical Care Clinics* (Maldonado 2008)

<table>
<thead>
<tr>
<th>Delirium Source</th>
<th>ACH</th>
<th>DA</th>
<th>GLU</th>
<th>GABA</th>
<th>SHT</th>
<th>NE</th>
<th>Trp</th>
<th>Phe</th>
<th>His</th>
<th>Cytok</th>
<th>HPA axis</th>
<th>NMDA activity</th>
<th>Changes in RBF</th>
<th>EEG</th>
<th>Mel</th>
<th>Inflam</th>
<th>Cort</th>
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<tr>
<td>Anoxia/hypoxia</td>
<td>↓</td>
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<td>Hepatic Failure</td>
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<td>Sleep deprivation</td>
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<tr>
<td>Trauma, Sx, &amp; Post-op</td>
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<tr>
<td>Etoh &amp; CNS-Dep Withdrawal</td>
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<td>DA agonist</td>
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<td>GABA use</td>
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<td>Dehydration &amp; Electrolyte Imbalance</td>
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</table>

**Legend:** ↑ = likely to be increased or activated; ↓ = likely to be decreased; ↔ = no significant changes; (†) = likely a contributor, exact mechanism is unclear; (-) = likely not to be a contributing factor; CVA = cerebro-vascular accident; Sx = surgery; Etoh = alcohol; CNS-Dep = central nervous system depressant agent; ACH = acetylcholine; DA = dopamine; GLU = glutamate; GABA = gamma-aminobutyric acid; 5HT = 5-hydroxytryptamine or serotonin; NE = norepinephrine; Trp = tryptophan; Phe = phenylalanine; His = histamine; Cytok = cytokines; HPA axis = hypothalamic-pituitary-adrenocortical axis; NMDA = N-methyl-D-aspartic acid; RBF = regional blood flow; EEG = electroencephalograph; Mel = melatonin; Inflam = inflammation; Cort = Cortisol.
Short-term alcohol intake produces a depression of the inhibitory centers of the cerebral cortex, which results in the initial symptoms of intoxication (euphoria, exaggerated feelings of well-being, and loss of self-control followed by sedation). Long-term alcohol intake causes the initial decrease with tolerance that occurs during continued exposure to alcohol. Removal of alcohol causes a rebound stimulatory effect, increasing excitability in the nervous system.

Adapted from Finn and Crabbe 1997
Fig. 1  Summary of receptor dysfunction in alcohol withdrawal: thin arrows (→) indicate the direction of relationships between alcohol withdrawal, inhibitory substances, excitatory transmitters and clinical symptoms; thick arrows indicate inhibition (↓) or excitation (↑) of receptor. (e.g. alcohol withdrawal results in a low concentration of Mg. Overactivity of NMDA receptors, due to this low Mg, can induce seizures and accentuate NA or DA release.)
Acute ETOH Use

- **GABA:** produces allosteric enhancement of GABAa receptors; contributing to many aspects of acute alcohol intoxication, including anxiety-reduction, sedation, and motor incoordination. Alcohol potentiates GABAa receptor signaling by increasing the frequency of channel opening events, mean open time, open time percentage, frequency of opening bursts, and the mean burst duration. Acute alcohol exposure also enhances the release of GABA from the presynaptic neuron, thus increasing GABA levels in the synaptic cleft and further activating the hypersensitive extrasynaptic receptors.

- **GLU:** inhibits NMDA, AMPA, kainate & Metabotropic GLU receptors. NMDA receptors are the most sensitive to alcohol inhibition. Modulation of glutamatergic function by ethanol contributes to both euphoric and dysphoric consequences of ethanol intoxication. GLU plays a significant role in all phases of alcoholism.
Acute ETOH Use

- **DA:** Disinhibit GABA-mediate DA projections to VTA→↑DA activity by direct excitatory DA VTA neurons & facilitates DA release by increasing opioidergic activity, further disinhibiting DA neurons, which further ↑extracellular DA activity in NA (likely responsible for impulse to drink).

- **NE:** Plasma and CSF NA and its major metabolite 3-methoxy-4-hydroxy phenylethylene glycol (MHPG) are increased by alcohol intoxication.

- **CA+ Ch:** inhibits voltage-gated Ca+ channels

- **5HT:** there is a dose-dependent increase in 5HT neurotransmission, in particular in NA, during acute alcohol intake→activates the mesolimbic dopaminergic reward system, further adding to the reinforcing actions of the alcohol.
Acute ETOH Use

- **HPA-axis**: is activated during alcohol intake via corticotrophin-releasing factor (CRF) to release cortisol and is important in mediating the continued urge to drink; glucocorticoids alter mesolimbic dopaminergic signaling, thus further amplifying the positive reinforcing effects of ETOH

- **MEL**: acute alcohol-induced dose-dependent attenuation of photic phase-delay shifts and serotonergic phase-advance shifts, where suprachiasmatic nucleus clock was demonstrated to be a direct target for disruptive effects of ethanol on photic shifting
Pathophysiology of Ethanol

- Agonistic effect at GABA_A receptors
- Disinhibits GABA-mediated DA projections to NA → DA → ↑ extracellular DA in NA; contributing to impulse to drink
- Inhibits GLU receptors
- ↑ of NE & its metabolite with acute intoxication
- Inhibition of voltage-gated Ca+ channels
- Dose-dependent increase in 5HT neurotransmission
- Activation of HPA via CRF → release cortisol; mediating the continued urge to drink; and altering mesolimbic dopaminergic signaling, further amplifying positive reinforcing effects of ETOH
- Attenuation of photic phase-delay shifts and disruption of melatonin release cycle

Maldonado et al, in Press
Chronic ETOH Use

- **GABA**: chronic alcohol use leads to counteradaptative responses that decrease GABA function. This is evident by both a decrease in the number of receptors and in changes in subunit composition that decrease receptor sensitivity. Prolonged enhancement leads to desensitization of GABAa receptors, internalization and down-regulation of GABAa receptors, especially in frontal lobes; also causes GABAa receptors to shift their composition to contain more α4 subunits, a formation that is less responsive to GABA signaling. Desensitization of the GABA$_A$ receptor, produced after chronic ethanol treatment, may be a necessary alteration that allows activation of the NMDA receptors.
Chronic ETOH Use

• **GLU**: increased synaptic glutamate (GLU) release; increased NMDA and non-NMDA (e.g., AMPA, kainate receptors) glutamatergic receptor activity; Chronic exposure of the brain to ethanol leads to up-regulation of the NMDA receptor and its responses and increases the number of glutamate binding site.

• **DA**: Chronic alcohol has been shown to cause a lowering in the basal and stimulated dopamine signal; with associated increased in DA availability.

• **NE**: In addition, chronic ethanol exposure leads to over activity of NE neurons in the central and peripheral nervous systems via desensitization of $\alpha_2$ receptors or lack of $\alpha2$ agonist activity and excessive NE production, as the excess extracellular DA is converted into NE via DA-$\beta$-hydroxylase.
Chronic ETOH Use

- **Ca+ Ch**: ↑ voltage-gated Ca channels receptor activity.
- **5HT**: Chronic use leads to down-regulation of 5HT1A receptors in hippocampus. Decreased expression of 5HT2 receptor genes in cerebral cortex and decreased 5HT uptake.
- **HPA-axis**: With chronic alcohol use, HPA axis becomes dysregulated as a result of initial super-excitation with the repeated intoxications leading to loss of a normal diurnal secretion pattern and hyporeactivity in cortisol response to physical and psychological stressors.
- **MEL**: Inversion of the circadian with abnormally elevated diurnal levels of melatonin
ETOH Withdrawal

- **GABA**: CSF examination reveal that GABA levels are low. Chronic exposure to alcohol produces many changes in the neurotransmission, leading to an overall reduced sensitivity to inhibitory signaling. The need for an increasing amount of alcoholic potentiation in order to maintain an inhibitory tone creates a hyperexcitable state within the central nervous system. Symptoms of alcohol withdrawal are due to this hyperexcitable state, including an increase in anxiety and seizures. While benzodiazepines are the primary therapeutic agent used to enhance GABA function during the hyperexcitable state of alcohol withdrawal, it is of little use on benzodiazepine-insensitive GABA\(_A\) receptors. **Desensitization of the GABA\(_A\) receptor can also contribute to activation of the NMDA receptors.** The reduction in GABAergic neuronal transmission and a rise in glutamatergic transmission during alcohol withdrawal may lead to CNS hyperexcitation leading to the development of agitation & seizures.
ETOH Withdrawal

- **DA:** DA levels on AWS-D#1 have been correlated with the severity of AWS as measured by CIWA-scores and pharmacological Tx needed. Upon AWS, excess DA leads to confusion, psychosis (hallucination, illusions, delusions), agitation, delirium. Data shows that patients with DTs demonstrated significantly higher plasma HVA than the control group, immediately preceding development of their psychotic symptoms.

- **GLU:** An increased NMDA receptor function is observed in chronic alcohol exposure, which produces a hyperexcitable state in alcohol withdrawal. There is a direct relationship between the increased NMDA receptor-channel complexes and the symptoms of AWS, particular AWSz. Upon AWS, excess GLU leads to confusion, psychosis (hallucination, illusions, delusions), agitation, delirium and seizure activity.
ETOH Withdrawal

- NE: Circulating levels of catecholamines are markedly elevated, leading to increases in cardiac output, stoke volume, and oxygen consumption. Human studies have confirmed that CSF levels of 3-methoxy-4-hydrophenylglycol (MHPG) were increased in patients undergoing alcohol withdrawal. Elevation in plasma free-MHPG concentration may similarly play a role in the evolution of delirium from non-alcohol withdrawal. ETOH inhibits the sensitivity of autonomic adrenergic systems, with a resulting up-regulation. During AWS, excess noradrenergic activity leads to the development of symptoms of autonomic hyperactivity (e.g., anxiety, agitation, tremor, sweating, hypertension, and tachycardia). ↑NE triggers neuronal damage by inducing imbalances btw cerebral O2 demand & supply→↑sensitivity of pyramidal neurons to excitatory effect of GLU & ↓perfusion. Also ↑NE→↑GLU. Increased NA levels may aggravate hypomagnesaemia (see above), thus producing another positive feedback loop.
ETOH Withdrawal

• **Ca+ Ch:** There is upregulation of dihydropiridine-sensitive L-type calcium channels during the acute withdrawal phase further leading to propagation of the excitation cascades.

• **5HT:** Serotonergic transmission appears to be decreased possibly leading to the dysphoria of alcohol withdrawal and alcohol cravings.

• **HPA:** HPA axis is activated once again during the alcohol withdrawal, leading to glucocorticoid elevation, particularly in prefrontal cortex and hippocampus, further potentiating the damage resulting from alcohol withdrawal. Glucocorticoids modulate ethanol withdrawal by exacerbating the glutamatergic cascade, possibly via activation of glucocorticoid receptors or increased number/function of NMDA receptors.

• **MEL:** Worsening of melatonin & circadian cycle reversal
Pathophysiology of Ethanol

Maldonado et al, in Press

Low GABA levels; accompanied by ↓GABA_A receptors function due to internalization and ↓ receptor sensitivity

↑↑↑DA leads to confusion, psychosis (hallucination, illusions, delusions), agitation, delirium

↑↑↑NMDA receptor-channel complexes activity → hyperexcitable state of AWS: confusion, psychosis (hallucination, illusions, delusions), agitation, delirium and seizure activity.

↑↑↑NA activity → SX autonomic hyperactivity (e.g., anxiety, agitation, tremor, sweating, hypertension, and tachycardia).

↑NA → ↑GLU & triggers neuronal damage by inducing imbalances btw cerebral O2 demand → ↑sensitivity of pyramidal neurons to excitatory effect of GLU

↑ voltage-gated Ca+ channels → propagation of the excitation cascades

Significantly ↓ 5HT neurotransmission → dysphoria

↑↑↑HPA via CRF → release cortisol; exacerbating the glutamatergic cascade & neuronal damage

Worsening of melatonin & circadian cycle reversal
Figure 1. Cellular Effects of Alcohol

EtOH = alcohol; R = receptor; G = guanine; AdCy = adenylate cyclase; Ad = adenosine; VGCC = voltage-gated calcium channel; GABA = gamma-aminobutyric acid; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; PKA = protein kinase A; PKC = protein kinase C; CaMKII = calcium-calmodulin kinase II.
Reproduced with permission from Fulton Crews.
# ETOH Neuromodulation

*Maldonado et al, in Press*

<table>
<thead>
<tr>
<th></th>
<th>GABA</th>
<th>GLUr</th>
<th>DA</th>
<th>NE</th>
<th>VGCC Ca+ Ch</th>
<th>5HT</th>
<th>HPA (CRF)</th>
<th>MEL</th>
<th>NGF</th>
<th>Mg+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>↑↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Chronic</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>AWS</td>
<td>↓↓</td>
<td>↑↑↑↑ (up to 300%)</td>
<td>↑↑↑↑</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↓↓↓</td>
<td>↑↑↑</td>
<td>↓</td>
</tr>
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</table>
Pathophysiology of Ethanol

ETOH (chronic consumption)

- Disinhibits GABA-mediated DA projections to NA → DA
- Inhibits NMDA receptors

↑ extracellular DA in NA
Is likely responsible for impulse to drink

- ↑ extracellular DA in NA
Is likely responsible for impulse to drink

- Adaptive suppression of GABA activity (internalization and down-regulation receptors)
- Glu/NMDA Dependent Confusion, psychosis (hallucination, illusions, delusions), agitation, delirium

- GLU/NMDA up-regulation & hypersensitization of NMDA receptors
- ↑ extracellular DA in NA
- Agonistic effect at GABA_A receptors
- Desensitization of α_2 receptors or lack of α2 agonist activity*

- A2-Agonists
- AntiGLU-ACA

- NE inhibits the sensitivity of autonomic adrenergic systems, with a resulting up-regulation

- Confusion, psychosis (hallucination, illusions, delusions), agitation, delirium
- APA

- Maldonado 2009
- Physical Sxix of W/D = excessive sympathetic drive

Li et al ‘01

Dependence
Seizures
Stanford Hospital & Clinics
Alcohol Withdrawal Prophylaxis & Treatment Protocol
Jose Maldonado, MD

Alcohol Use within the last 30 days; or a *+* Blood Alcohol Level (BAL)?

YES

Perform PAWSS
(Prediction of Alcohol Withdrawal Severity Scale)
(Maldonado 2011)

LOW RISK
No immediate intervention needed

< 3

HIGH RISK
Perform AWSS or CIWA

≥ 3

AWS ≤ 5
CIWA-Ar ≤ 15

Either

Withdrawal Prophylaxis Protocols

Either

PROTOCOL A
Non-SZDP Prophylaxis Protocol

Symptoms progression: assessed by clinical picture & worsening AWS (AWS ≥ 6; CIWA-Ar ≥ 16)
Switch to Tx Protocol (C or D)

PROTOCOL B
Lorazepam Fixed Prophylaxis Protocol

PROTOCOL C
Non-SZDP Treatment Protocol

Symptoms progression: assessed by clinical picture & worsening AWS (AWS ≥ 10; CIWA-Ar ≥ 20)
Switch to Tx Rescue Protocol

PROTOCOL D
Lorazepam Ser-Triggered Treatment Protocol

PROTOCOL E
In case of DTs not responding to conventional Tx consider transfer to ICU
[i.e., AWSS ≥ 10, CIWA-Ar ≥ 20]

Rescue Protocol E

Surveillance Mode
Repeat assessment scale q.4 hrs

Withdrawal Treatment Protocols

Either
### Alcohol Withdrawal Assessment Scale (AWSS)

#### Somatic (S) Subscale: Somatic symptoms

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate/ min</td>
<td>&lt;100</td>
<td>101 – 110</td>
<td>111 – 120</td>
<td>&gt;120</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>&lt;95</td>
<td>96 – 100</td>
<td>101 – 105</td>
<td>&gt;105</td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>&lt;37.0</td>
<td>37.0 – 37.5</td>
<td>37.6 – 38.0</td>
<td>&gt;38.0</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate/min</td>
<td>&lt;20</td>
<td>20 – 24</td>
<td>&gt;24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perspiration</td>
<td>None</td>
<td>Mild (wet hands)</td>
<td>Moderate (forehead)</td>
<td>Severe (profuse)</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>None</td>
<td>Mild (mildly raised &amp; finger spread)</td>
<td>Moderate (fingers spread)</td>
<td>Severe (spontaneous)</td>
<td></td>
</tr>
</tbody>
</table>

#### Mental (M) Subscale: Mental symptoms

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>None</td>
<td>Fastening</td>
<td>Rolling in bed</td>
<td>Try to leave bed</td>
<td>In rage</td>
<td></td>
</tr>
<tr>
<td>Contact</td>
<td>Short talk possible</td>
<td>Easily distractible</td>
<td>Drifting contact</td>
<td>Dialogue impossible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orientation (time, place, person, situation)</td>
<td>Fully aware</td>
<td>One sphere disturbed</td>
<td>Two spheres disturbed</td>
<td>Totally confused</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>None</td>
<td>Uncertain</td>
<td>One kind present</td>
<td>Two kinds present</td>
<td>All kinds</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>None</td>
<td>Mild (only if asked)</td>
<td>Moderate (spontaneous complaint)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Subscore of somatic symptoms →

#### Subscore of mental symptoms →

#### Total score T = S + M →

### CIWA-Ar

(Sullivan et al 1989; Shaw et al 1981; Hollbrock’99)

<table>
<thead>
<tr>
<th>CIWA-Ar</th>
<th>AWSS</th>
</tr>
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<tbody>
<tr>
<td>Mild</td>
<td>≤ 15</td>
</tr>
<tr>
<td>Moderate</td>
<td>16–20</td>
</tr>
<tr>
<td>Severe</td>
<td>≥ 20</td>
</tr>
<tr>
<td>Patient</td>
<td>BAL</td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
</tr>
<tr>
<td>37 M</td>
<td>446</td>
</tr>
<tr>
<td>46 M</td>
<td>382</td>
</tr>
<tr>
<td>32 M</td>
<td>71.4</td>
</tr>
<tr>
<td>51 M</td>
<td>360</td>
</tr>
<tr>
<td>45 M</td>
<td>Not done (prior 200s-300s)</td>
</tr>
<tr>
<td>58 M</td>
<td>367</td>
</tr>
<tr>
<td>50 M</td>
<td>335</td>
</tr>
<tr>
<td>62 F</td>
<td>35 (prior 200s-300s)</td>
</tr>
<tr>
<td>66 F</td>
<td>47</td>
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</table>
An Approach to the Patient with Substance Use and Abuse

Jose R. Maldonado, MD

Keywords
- Substance use
- Substance abuse

Substance use is ubiquitous among men and women. The National Survey on Drug Abuse and Health (SAMHSA) reported in 2019 that 60% of the US population aged 12 years or older (49%) had used or attempted to use a psychoactive substance in the past year. Of these, marijuana was the most commonly used (7.4 million users), followed by cocaine (1.5 million), and heroin (300,000). Substance use disorders (SUDs) are among the most prevalent mental health conditions, affecting up to 23 million Americans annually.

Current Approaches to the Recognition and Treatment of Alcohol Withdrawal and Delirium Tremens: “Old Wine in New Bottles” or “New Wine in Old Bottles”

Th. M. Stern, MD; Anne E. Gainer, MD; Arsh K. Sandeep; Shams H. Najjar, MD; Jose R. Maldonado, MD

are you ever wondered: how much alcohol a person has to drink (and for how long) before he or she develops a withdrawal symptom after sudden abstention? Have you ever wondered which people are best in diagnosing and quantifying the severity of alcohol withdrawal? How do you think about what strategies can help with alcohol withdrawal? If you have, then the following discussion of the literature should serve as a way to enhance your understanding of the problem and to create effective solutions.

November: How Has Alcohol Withdrawal Been Viewed?

A retrospective analysis of alcohol withdrawal, including delirium tremens (DT), has the medical literature since the late 1700s. Despite later in the 1970s the modified DSM-III criteria for alcohol withdrawal and delirium tremens, the association between alcohol withdrawal and delirium tremens has been a matter of dispute. The understanding of these conditions is still evolving. The term “alcohol withdrawal” has been used in a consistent setting since 1961. It is not clear whether symptoms are related to the creation of alcohol consumption.

“Novel Alcohol Withdrawal Treatment Methods - Beyond Benzodiazepines”

Jose R. Maldonado, MD, FAPM, FACPE

Address: University of Medicine & Dentistry of New Jersey, Newark, NJ 07103, USA

Objective: To evaluate the safety and efficacy of clonazepam and lorazepam for the treatment of alcohol withdrawal and delirium tremens.

Methods: A randomized, double-blind, placebo-controlled trial was conducted at a Veterans Affairs Medical Center in New Jersey. Patients were randomized to receive clonazepam (n = 45) or lorazepam (n = 45) for treatment of alcohol withdrawal and delirium tremens. The primary outcome measure was the number of patients who experienced a reduction of at least 50% in the NIAAA Alcohol Withdrawal Scale (AWAS) score from baseline to day 3.

Results: The mean AWAS score at baseline was 22.0 ± 2.3 in the clonazepam group and 21.5 ± 2.4 in the lorazepam group. At day 3, the mean AWAS score was 7.5 ± 2.1 in the clonazepam group and 8.0 ± 2.2 in the lorazepam group. The difference in AWAS scores between the two groups was not statistically significant (p = 0.39). There were no statistically significant differences in the incidence of adverse events between the two groups.

Conclusion: Clonazepam and lorazepam are effective and safe for the treatment of alcohol withdrawal and delirium tremens. Further studies are needed to confirm these findings.

References:


Hair of the Dog: 
Pathophysiology of Alcohol Withdrawal 
& Foundations of Treatment

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