Appendix

I. DSM-V Criteria: Alcohol Use Disorder
II. Bonnet, et al. (1999)
III. Bonnet, et al. (2003)
IV. Mariani, et al. (2006)
V. Myrick, et al. (2009)
VI. Bonnet, et al. (2010)
I. DSM-V Criteria for Alcohol Use Disorder

A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.
    b. A markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for alcohol (refer to Criteria A and B of the criteria set for alcohol withdrawal, pp. 499-500).
    b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

Specify if:
In early remission: After full criteria for alcohol use disorder were previously met, none of the criteria for alcohol use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, “Craving, or a strong desire or urge to use alcohol,” may be met).
In sustained remission: After full criteria for alcohol use disorder were previously met, none of the criteria for alcohol use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, “Craving, or a strong desire or urge to use alcohol,” may be met).

Specify if:
In a controlled environment: This additional specifier is used if the individual is in an environment where access to alcohol is restricted.

Specify current severity:
305.00 (FI 0.10) Mild: Presence of 2-3 symptoms.
303.90 (FI 0.20) Moderate: Presence of 4-5 symptoms.
303.90 (FI 0.20) Severe: Presence of 6 or more symptoms.
II. Treatment of Alcohol Withdrawal Syndrome with Gabapentin

Objective
To describe the case of four inpatients with moderate alcohol withdrawal syndrome (AWS) that benefited from gabapentin administration in an add-on fashion to clomethiazole

Study Design

- Case Report
- Population Characteristics:
  - Three men and one woman
  - Mean age 36, range 30-46
  - DSM-IV criteria for alcohol dependence for over five years
  - Had seizures due to alcohol withdrawal in their past medical history
  - Breath Alcohol Concentration (BAC) greater than 0.25% on admission
  - Self-reported daily alcohol consumption > 220 g ethanol for more than 12 weeks prior to detox
  - All patients smokers (greater than 20 cigs per day)
  - No history of illicit drug use
  - The three male patients had detoxed at hospital in past on clomethiazole alone

Methods

- After BAC < 0.1%, in initial 24 hours of detox, the items tachycardia, hypertension, agitation, tremor, hyperhidrosis, and anxiety were rated every hour and scored; measurements repeated every hour
  - Sum score 4-6 points: 1 capsule of clomethiazole
  - Sum score 7-9 points: 2 capsules of clomethiazole
- After initial 24 hours, patients proceeded to “reduction phase”
  - Clomethiazole dose reduced by 2 capsules daily
- Day 1 of admission, patients received 400 mg of gabapentin after BAC < 0.15%, then 400 mg given Q6H in first 48 hours
  - Starting third day, daily dose of gabapentin reduced by 400 mg daily
  - When BAC < 0.1%, patients could receive clomethiazole PRN via severity score (see above)

Results

- Gabapentin clearly led to reduction in clomethiazole requirements
  - Patient 1: 13-20 clomethiazole capsules previously (2 prior detox) vs. 0 clomethiazole capsules with gabapentin
  - Patient 2: 19 clomethiazole capsules previously (1 prior detox) vs. 7 clomethiazole capsules with gabapentin
  - Patient 3: 14-21 clomethiazole capsules previously (4 prior detox) vs. 10 clomethiazole capsules with gabapentin
  - Patient 4: Data unavailable
- Seizures did not occur in any of the four inpatients
  - Patients 1 & 2 had 2 withdrawal-related seizures from previous hospitalizations
  - Patient 3 had 1 prior withdrawal-related seizure
- No adverse effects occurred, with the exception of fatigue in one patient
- No deterioration in liver enzymes, CBC, or amylase levels

Strengths and Limitations

- Strengths: first study to demonstrate possibility that gabapentin used adjunctively can reduce rescue medication
- Limitations: case study, need for more baseline information (were patients drinking same amount as previous admission?)

Conclusion
Gabapentin has future potential in treatment of moderate-severe AWS and deserves further controlled studies
Objective

To evaluate the efficacy of gabapentin 400 mg QID in the treatment of acute AWS

Study Design

- 2-center (psychiatric hospitals in Germany), double-blind, placebo-controlled
- Inclusion Criteria:
  - Suffered from alcohol dependence (ICD-10)
  - Mainz Alcohol Withdrawal Score (MAWS) $\geq 4$
  - Negative urine drug screen
- Exclusion Criteria:
  - Psychiatric condition requiring medication
  - Abuse or dependence of other substances
  - Relevant medical conditions
  - Pregnant or nursing
  - Current use of: BZDs, lithium, disulfiram, beta-blockers, neuroleptics, anticonvulsants, antidepressants, or antacids

Methods

- Acute Part 1:
  - First capsule of study medication 400 mg of gabapentin (n=32) or placebo (n=29) given at baseline
  - Study medication then administered Q6H during next 24 hours
  - When BAC < 0.1%, clomethiazole administered as-needed based on severity score
    - Tachycardia, hypertension, tremor, hyperhidrosis, and anxiety rated every hour and scored
    - 4-6 points = 1 capsule; 7-9 points = 2 capsules
- Acute Part 2:
  - Study medication continued Q6H in following 24 hours
  - Amount of clomethiazole as-needed reduced by 2 capsules each day
  - After third day of detoxification, study medication reduced by 1 capsule each day

Results

- Baseline Characteristics:
  - Majority of patients male (70.5%)
  - Mean age 44.3 ± 7.5 years
  - Mean daily alcohol consumption 360 ± 163 grams/day
  - Mean previous inpatient detoxifications = 2
  - MAWS score: 6
- Primary: no difference in amount of clomethiazole required in first 24 hours (n=57) (P=0.96)
- Secondary: no difference in decrease in MAWS between groups (P=0.26); difference not seen in post-hoc analysis
- No patients developed seizures or delirium during treatment
- Six patients taking placebo vs. five taking gabapentin experienced adverse-effects (vertigo, nausea, dizziness, ataxia)

Strengths and Limitations

- Strengths: more baseline information, controlled-study, easy to replicate
- Limitations: small sample-size, gabapentin dose potentially too low, clomethiazole could have masked gabapentin effects

Conclusion

Gabapentin 400 mg QID is no better than placebo in reducing the need for rescue clomethiazole for treatment of AWS
Objective

To assess the efficacy of gabapentin in the management of alcohol withdrawal

Study Design

- Single-center, open-label, randomized, controlled clinical trial (inpatient)

  - Inclusion Criteria:
    - Between 18-60 years old
    - DSM-IV diagnosis of alcohol dependence
    - Clinical Institute for Alcohol Scale-Revised (CIWA-Ar) score of 10 or higher (i.e. moderate alcohol withdrawal)

  - Exclusion Criteria:
    - Presence of other DSM-IV Axis I non-substance related psychiatric disorders
    - Severe unstable medical illness (heart disease, diabetes, epilepsy, cirrhosis)
    - Presence of alcohol withdrawal related delirium
    - Coexisting use of opioids or sedative-hypnotic agents (excluding methadone maintenance treatment)

Methods

- Gabapentin group (n=14)
  - Day 1: 1200 mg load, followed by 600 mg Q6H for two doses (2400 mg in initial 24 hours)
  - Day 2: 600 mg TID; Day 3: 600 mg BID; Day 4: 600 mg daily

- Phenobarbital group (n=13)
  - Day 1: 60 mg QID; Day 2: 60 mg TID; Day 3: 60 mg BID; Day 4: 30 mg BID

- Both groups received phenobarbital 60 mg by mouth on as-needed basis for breakthrough withdrawal symptoms
  - HR > 100, SBP > 150 mmHg, agitation, temperature > 100.5°F, diaphoresis, tremor

- Gabapentin patients requiring ≥3 doses phenobarbital transferred to phenobarbital group and labeled treatment failure

Statistical Analyses

- Independent t-test for baseline and mean CIWA-Ar scores, and rating scale scores
  - Results of parametric statistics confirmed with non-parametric statistics

- Fisher’s exact test to compare % subjects successfully completing treatment and % requiring rescue doses of phenobarbital

Results

- No differences in baseline characteristics or rating scales (including baseline CIWA scores=19-20)
- Proportion of patients requiring PRN phenobarbital no different between groups (57% gabapentin vs. 38% phenobarbital; P=0.45); patients on gabapentin receiving more PRN phenobarbital had significantly higher CIWA scores (P=0.02).
- No difference in ‘treatment failures’ (≥3 PRN doses phenobarbital)
- No differences in HAM-A, POMS, dysphoria, irritability, sleep problem score, or hours of sleep between groups
- No difference in % of patients remaining inpatient during detox period (79% gabapentin, 77% phenobarbital; P=1.0)
- No serious adverse events recorded; no withdrawal seizures of alcohol withdrawal delirium occurrences

Strengths and Limitations

- Strengths: randomized, controlled trial, use of multiple rating scales to assess progression of treatment
- Limitations: comparator not recommended for alcohol withdrawal and may have confounded gabapentin effects

Conclusion

Gabapentin may be equivalent to phenobarbital in the treatment of alcohol withdrawal
V. A Double-Blind Trial of Gabapentin Versus Lorazepam in the Treatment of Alcohol Withdrawal

Objective
To evaluate alcohol use and symptom reduction of gabapentin compared to lorazepam in the treatment of alcohol withdrawal

Study Design

- Single-center, double-blind, dose-response trial (outpatient)
- Inclusion Criteria:
  - DSM-IV criteria for alcohol dependence and alcohol withdrawal
  - Blood alcohol level 0.1 g/dl or less
  - Mini-mental-state exam (MMSE) score ≥ 26
  - CIWA-Ar ≥ 10
- Exclusion Criteria:
  - All substance use disorders except alcohol dependence, nicotine dependence, or cannabis abuse
  - Major Axis I psychiatric disorder
  - Use of medication in preceding 30 days that could alter withdrawal process (BZDs, beta-blockers, neuroleptics)
  - History of head injury or other neurological illness including idiopathic epilepsy
  - Medical instability, ECG abnormalities

Methods

- Patients stratified to two groups based on number of previous medical detoxifications
- Gabapentin group received one of three dosing regimens:
  - 600 mg (200 mg TID) tapered to 400 mg (200 mg BID) on day 4 **terminated after first 6 participants**
  - 900 mg (300 mg TID) tapered to 600 mg (300 mg BID) on day 4 (n=28)
  - 1200 mg (400 mg TID) tapered to 800 mg (400 mg BID) on day 4 (n=28)
- Lorazepam group received 6 mg (2 mg TID) for 3 days then tapered to 4 mg (2 mg BID) on day 4 (n=28)
- Blinded rescue medication packs given to each participant on days 1 to 4
  - Gabapentin group rescue pack provided two 100 mg doses and one 300 mg dose for evening use on day 1
    - Days 2 to 4 rescue pack had three 100 mg doses
  - Lorazepam rescue pack provided two 1 mg doses and one 2 mg doses for evening use on day 1
    - Days 2 and 4 rescue pack had three 1 mg doses

Statistical Analyses
- CIWA-Ar scores analyzed as a mixed model with an unstructured variance/covariance mix

Results

- No significant difference in baseline demographics between groups (baseline CIWA scores=12-14)
  - High-dose gabapentin subjects ingesting about 5 drinks more per day than the other groups (P=0.041)
- No significant difference in the number of rescue doses needed between groups (P=0.75)
- High-dose gabapentin group (P=0.009), but not low-dose (P=0.62), had lower CIWA-Ar scores than the lorazepam group over first four treatment days
  - Significant difference in both treatment and follow-up phase (P=0.03 and P=0.006)
- Probability of drinking during treatment higher in lorazepam group after day 1 (0.027)
- Craving significantly reduced in gabapentin group compared to lorazepam group at both doses during medication period
- Lower Zung Anxiety Scale scores lower in both gabapentin groups (P<0.05) and Beck Depression Inventory scores in 900 mg gabapentin group
- No difference in self-reported side-effects between groups (P=0.74)
Strengths and Limitations

- **Strengths**: first double-blind trial, use of both lower and higher gabapentin dose, using rescue gabapentin, evaluated risks of drinking relapse and craving in addition to rescue medication needs and CIWA-Ar reduction
- **Limitations**: small-sample size (large compared to previous trials), only mild-moderate AWS severity

**Conclusion**

Gabapentin found to be superior to lorazepam in the treatment of outpatients (lower probability of drinking and clinically similar symptom reduction)
VI. An Open Trial of Gabapentin in Acute Alcohol Withdrawal Using an Oral Loading Protocol

Objective

To test a higher gabapentin entry dose (800 mg loaded up to 3200 mg in first 24 hours) for the treatment of severe acute AWS

Study Design

- Single-center, open-label trial (inpatient)
- Inclusion Criteria:
  - Diagnosis of alcohol dependence displaying severe AWS (CIWA-Ar ≥ 15)
  - Age between 18 and 70
- Exclusion Criteria:
  - Psychiatric or somatic comorbidities requiring acute intervention or stabilization
  - Pregnancy
  - Delirium tremens
  - Severe cognitive deficits
  - Coexisting substance use disorders (except nicotine)
  - Current use of: BZDs, z-drugs, lithium, disulfiram, beta-blockers, neuroleptics, anti-convulsants, antidepressants

Methods

- Entry dose of gabapentin 800 mg given at baseline (CIWA-Ar ≥ 15, BAC < 0.2%)
- If AWS improved within next 2 hours (CIWA-Ar < 15), patients classified as ‘early-responders’
  - Day 1: 3200 mg in first 24 hours; Day 2: 600 mg QID; Day 3: 400 mg QID; Day 4: taper down by 400 mg daily
- If CIWA-Ar did not improve or worsened in 2 hours, patients defined as ‘early non-responders’
  - Treatment as usual (clomethiazole or clonazepam)

Statistical Analyses

- Statistical analysis not described; ANOVA used to evaluate decline of CIWA-Ar values

Results

- No baseline differences between groups in regards to drinking history or alcohol-related sequelae (baseline CIWA=19-20)
- Significant decline in CIWA-Ar in ‘early-responders’ group; largest decline within 2 hours after entry dose (from 17.3 ± 2.6 points to 8.0 ± 3.6 points; P<0.001); non-responders declined from 20.1 ± 4.6 to 21.5 ± 4.6 points following gabapentin load
  - Two early-responders developed seizures, one developed worsening AWS in following 36 hours
    - Reclassified as ‘non-responders’ and switched to clonazepam
- Treatment days 10.6 ± 3.6 days in ‘early-responders’ group vs. 14.4 ± 7.9 days in ‘non-responders’ group (P=0.05)
- HAMA and HAMD scores improved from 10.5 ± 6.5 points and 10.8 ± 5.1 points to 3.1 ± 4.8 points (P<0.001) and 3.6 ± 3.7 points (P<0.001) in ‘early-responders’ group vs. 20.1 ± 3.5 points and 20.3 ± 4.2 points to 12.6 ± 7.7 points (P=0.001) and 11.4 ± 6.8 points (P<0.001) in ‘non-responders’ group
- 22.2% of ‘early-responders’ vs. 50% of ‘non-responders’ experienced clinical adverse effects (all considered mild)

Strengths and Limitations

- Strengths: high baseline severity of AW, higher doses of gabapentin tested (load of 3200 mg in one day)
- Limitations: very small sample size, open-label trial, no active comparator

Conclusion

Non-response to gabapentin can be predicted by more severe AW (CIWA score >20) with greater anxiety/depressive symptoms