

The AMAZING
CARBAMAZEPINE

Is there a Role in Acute Alcohol
Withdrawal?

Michelle Hinch, BSc Pharm

Doctor of Pharmacy Student, UBC

Jan 31, 2012

The Many Roles of Carbamazepine

- Anticonvulsant
- Neuropathic pain
- Trigeminal neuralgia
- Bipolar disorder
- Schizophrenia
- Post traumatic stress disorder
- Alcohol withdrawal??

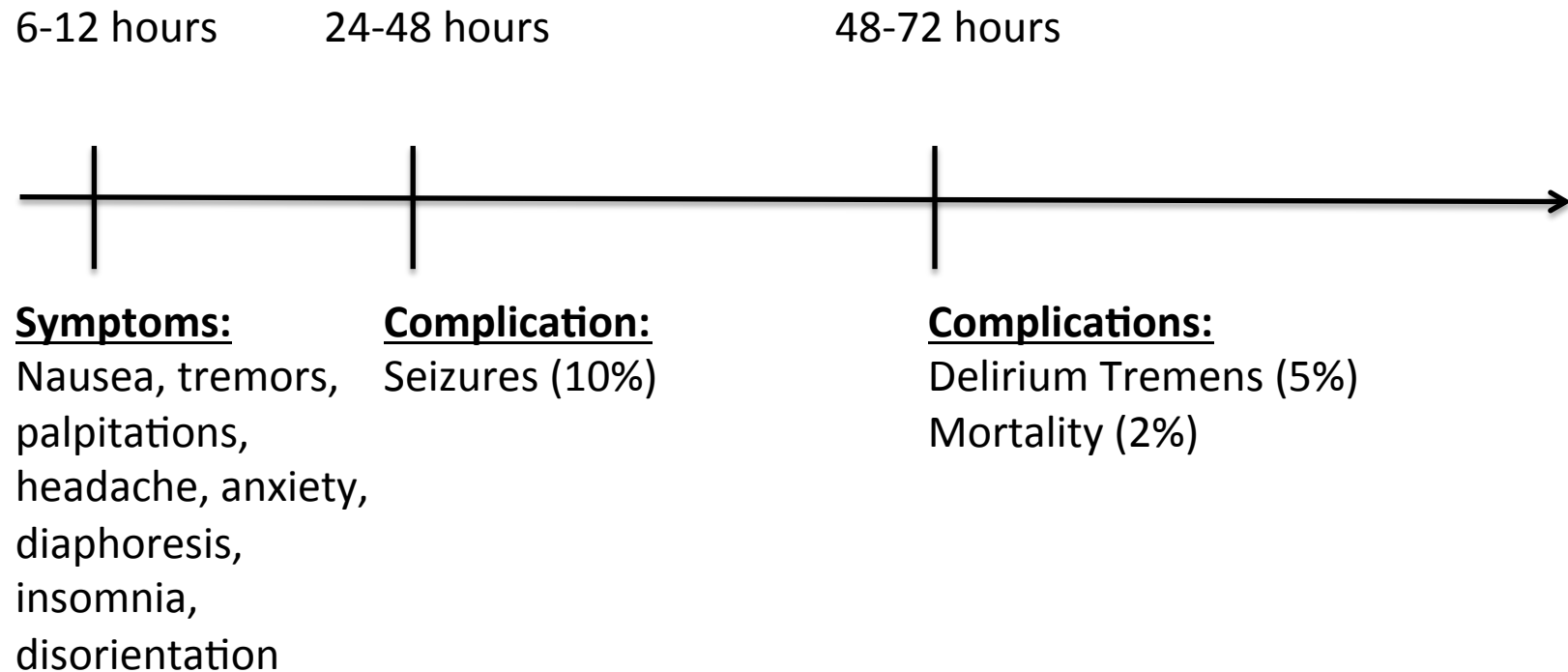
Current Practice – Treatment of Alcohol Withdrawal

- Symptom triggered dosing of benzodiazepine (BZD): diazepam or lorazepam
 - Cessation of chronic alcohol consumption leads to hyper-excitable state in CNS
- Dosing Q1H PRN based on Clinical Institute Withdrawal Assessment – Alcohol-revised (CIWA-Ar) scale
- Used to control symptoms of withdrawal, and prevent seizures and delirium tremens (DTs)

JAMA. 1994;272:519–23.

Brit J Addiction 1989;84(11):1373–1357

Onset of Symptoms after Chronic Alcohol Cessation



Interpretation of CIWA-Ar

Cumulative Score:

- <8-10 Mild Withdrawal; no medication necessary, supportive care only
- 10-15 Moderate withdrawal; require symptom management
- >15 Severe withdrawal; significant risk of major complications if untreated
- 67 Maximum possible cumulative score

Concerns with the Use of BZD

- Additive effects with alcohol
 - Sedation, respiratory depression
- Cognitive impairment
- Abuse potential
- Refused admission to half-way houses for continued detox
 - Compromises rehabilitation efforts

Is There a Role for Carbamazepine?

Mechanism of action:

- Possesses GABAnergic activity and blocks NMDA receptors

Advantages compared to BZDs:

- No abuse potential
- No respiratory depression
- Does not potentiate alcohol intoxication

Is There a Role for Carbamazepine?

Disadvantages compared to BZDs

- CYP3A4 drug interactions
- Limited routes of administration

Clinical Question

Patients	Chronic alcoholics undergoing acute alcohol withdrawal
Intervention	Carbamazepine
Comparator	Benzodiazepines
Outcomes	<u>Efficacy:</u> Reduction in symptoms Prevention of Delirium Tremens Prevention of Seizures Prevention of Mortality <u>Toxicity:</u> Adverse effects – sedation, ataxia, nausea, pruritus, leukopenia

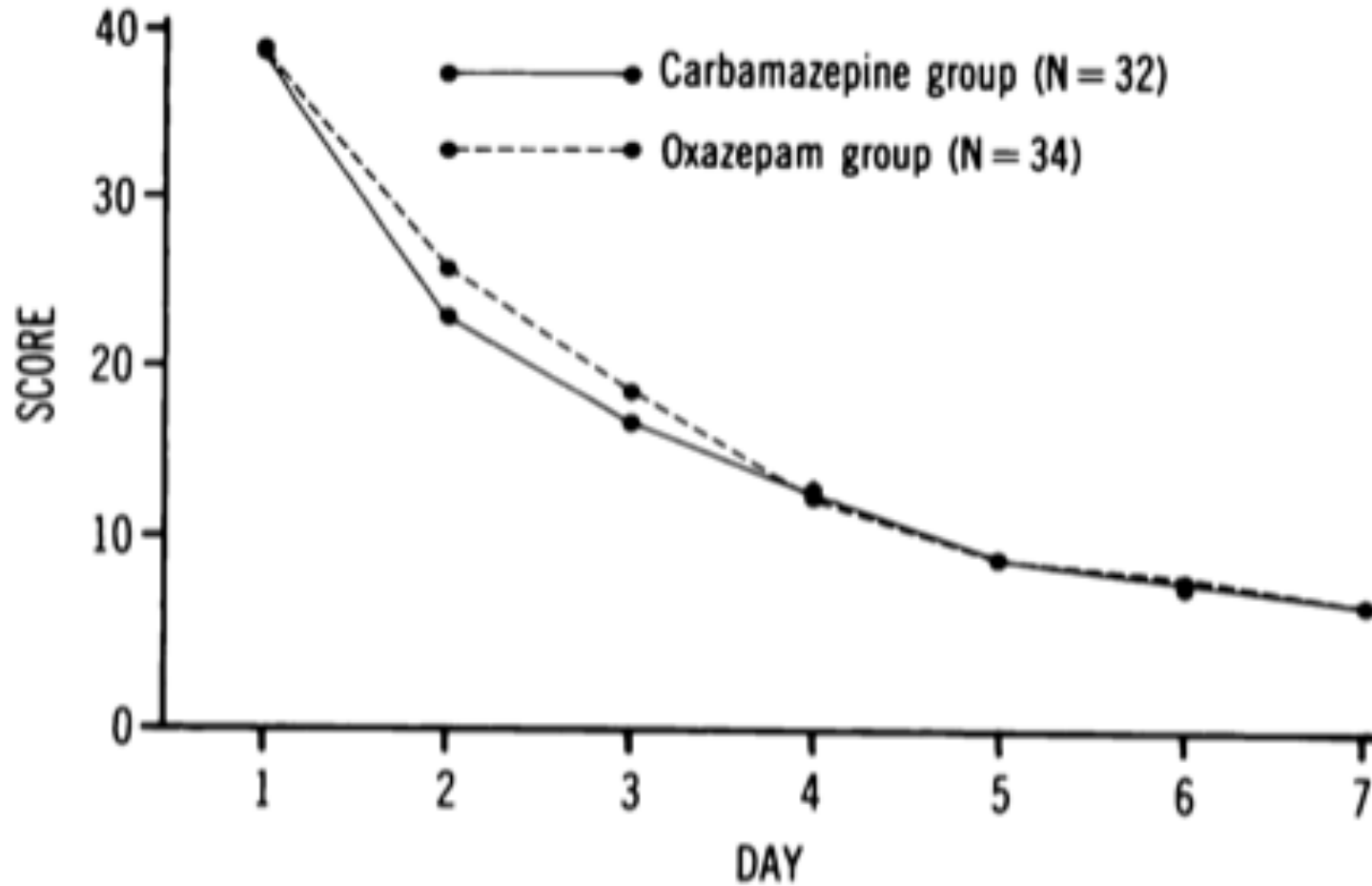
Search Strategy

Databases	Embase, Medline, Pubmed, Google Scholar
Search terms	Carbamazepine AND substance withdrawal syndrome OR alcohol withdrawal delirium
Limits	Human, English
Exclusions	Trials with BZD adjunct to carbamazepine
Results	3 RCTs 1 abstract

Malcolm et al, 1989

D	SC, DB, RCT
P	<u>Inclusion:</u> n=86; inpatient males; age 18-65; CIWA-A \geq 20; DMS-III criteria for alcohol dependency <u>Exclusion:</u> daily use of CNS active drugs or illicit drugs, mental illness, LFTs >2.5 x ULN, DM, CRF, neurologic disease
I	Carbamazepine 200mg PO QID x 7 days
C	Oxazepam 30mg PO QID x 7 days
O	Alcohol withdrawal severity: CIWA-A Psychological testing (overall distress, depression, anxiety, mental functioning): SCL-90-R

Malcolm et al - Results



Malcolm et al - Results

	Carbamazepine	Oxazepam
CIWA-A	NSS at any time point	
SCL-90-R	Mean score equivalent on day 3; Day 7 – “increase in score for oxazepam, decrease for CMZ”	
DTs	Not reported	Not reported
Seizures	Not reported	Not reported
Mortality	None	None
Adverse Effects		
• Sedation	NSS	NSS
• Ataxia	NSS	NSS
• Pruritus	Not reported	Not reported
• Nausea/vomiting	NSS	NSS

Malcolm et al - Conclusions

- “carbamazepine is as effective as oxazepam in the treatment of substantial alcohol withdrawal in hospitalized male alcoholics”
- “We did not find advantages of carbamazepine substantial enough to warrant its routine replacement of benzodiazepines”

Malcolm et al - Strengths

- High CIWA-A score at baseline
- Did not excluded patients with a prior history of seizures

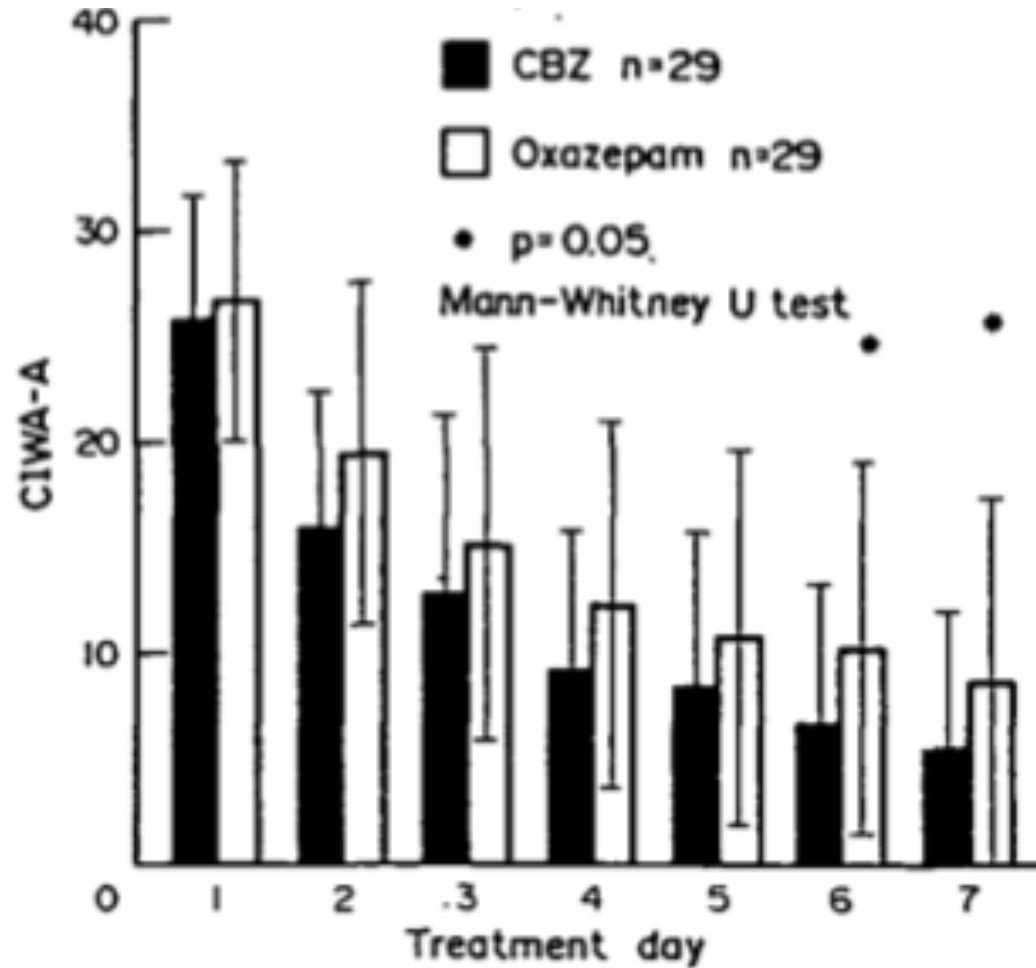
Malcolm et al - Limitations

- 23% dropout rate
 - only 66 patients completed trial; needed 80-100 patients to detect 10% difference between the groups
- Fixed dose vs. symptom triggered oxazepam
- Use of older CIWA-A scale vs. CIWA-Ar
 - 15 item vs. 10 item rating scale
- Recorded CIWA-A scores twice daily
- Inclusion of male patients only
- Do not report baseline characteristics of patients

Stuppaeck et al, 1992

D	SC, DB, RCT
P	<u>Inclusion</u> : n=60; CIWA-A \geq 20; inpatients; age 18-65; DMS-III criteria for alcohol dependency <u>Exclusion</u> : cirrhosis, epilepsy, poly-substance dependence, full-blown withdrawal delirium, pretreatment with psychotropic substances
I	CMZ PO 800mg/day Days 1-3, then 600mg/day Days 4-7
C	Oxazepam PO 120mg/day Days 1-3, then 90mg/day Days 4-7
O	Withdrawal Severity: CIWA-A (daily at 5PM) Clinical Global Impression Scale: Days 1,4, and 7 Self rating score

Stuppaeck et al - Results



Stuppaeck et al - Results

	Carbamazepine n=16 Patients (%)	Oxazepam n=12 Patients (%)
CIWA-A	SS difference on Days 6 and 7 in favor of CMZ	
CGI score	SS difference on day 7 in favor of CMZ	
DTs	None	2 (16.7%)
Seizures	None	1 (8.3%)
Mortality	None	None
Adverse Effects		
• Sedation	7 (43.8%)	5 (41.7%)
• Ataxia	3 (18.8%)	0%
• Pruritus	6 (37.5%)	2 (16.7%)
• Nausea/vomiting	3 (18.8%)	0%

Stuppaeck et al - Results

	Carbamazepine n=16 Patients (%)	Oxazepam n=12 Patients (%)
CIWA-A	SS difference on Days 6 and 7 in favor of CMZ	
CGI score	SS difference on day 7 in favor of CMZ	
DTs	None	2 (16.7%)
Seizures	None	1 (8.3%)
Mortality	None	None
Adverse Effects		
• Sedation	7 (43.8%)	5 (41.7%)
• Ataxia	3 (18.8%)	0%
• Pruritus	6 (37.5%)	2 (16.7%)
• Nausea/vomiting	3 (18.8%)	0%

Stuppaeck et al - Conclusions

- “The efficacy of carbamazepine in AWS is beyond any doubt.”
- “Carbamazepine seems to be superior during the whole trial period. . .”

Stuppaeck et al – Strengths and Limitations

Strengths

- Inclusion of female patients
- High CIWA-A scores at baseline
- No inter-rater variability on CIWA-A score assessment

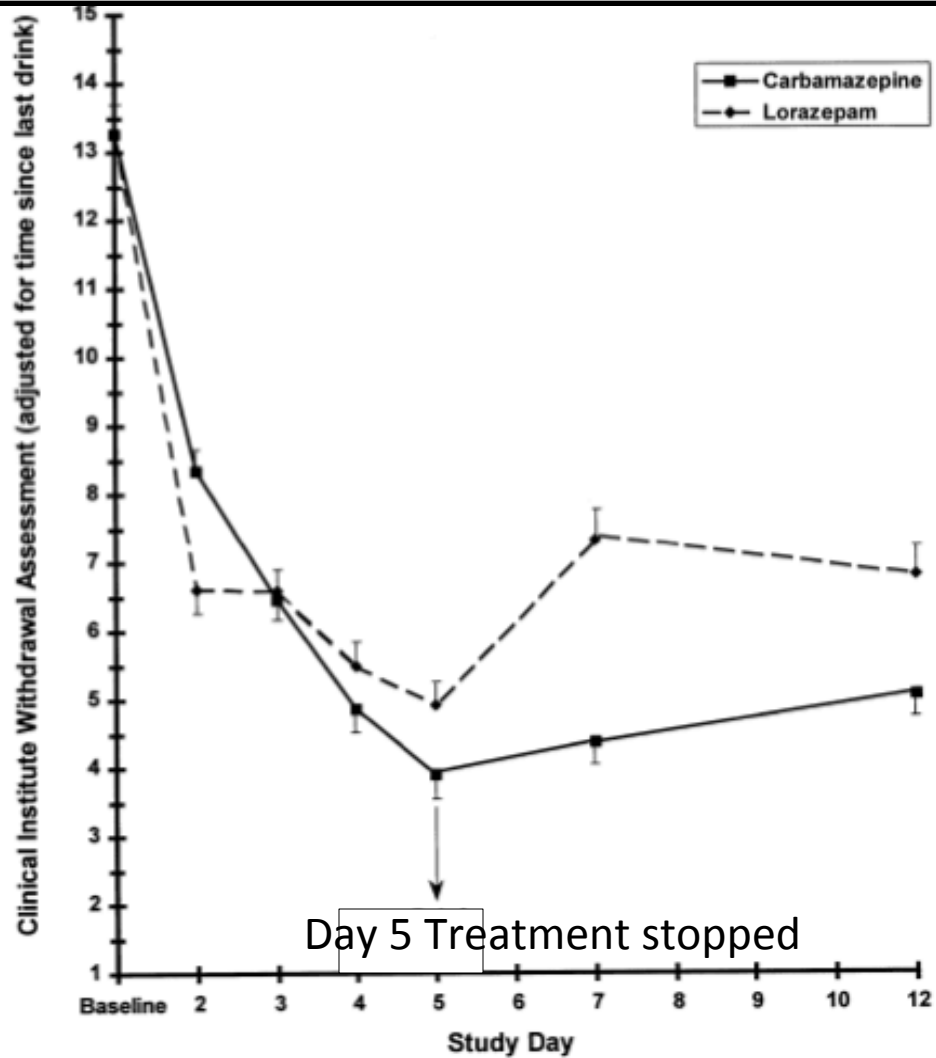
Limitations

- Fixed dose vs. symptom triggered oxazepam
- Use of CIWA-A scale
- No power calculation; no indication of study design
- Only assessing patients once daily; not indicating timing in relation to medication dose

Malcolm et al, 2002

D	SC, DB, RCT
P	Inclusion: n=136; outpatients; CIWA-Ar score ≥ 10 ; blood alcohol level $\leq 0.1\text{g/dL}$; DMS-IV criteria for alcohol dependence Exclusion: substance abuse, major Axis I disorders, history of head injury or epilepsy, medical instability, EEG abnormality; LFTs $>3\text{x}$ ULN
I	CMZ 600-800mg/d x 1 day, then tapered until 200mg/day on day 5
C	Lorazepam 6-8mg/d x 1 day, then tapered until 2mg/day on day 5
O	Alcohol Withdrawal: CIWA-Ar once daily x 5 days, and Day 7 & 12 Alcohol Consumption post discharge Side Effects

Malcolm et al



Malcolm et al - Results

	Carbamazepine	Oxazepam
CIWA-Ar	1. No difference over 12 days ($p \leq 0.23$) 2. A difference by treatment group over time ($p \leq 0.007$) 3. A difference on Day 7 ($p \leq 0.01$)	
DTs	None	None
Seizures	None	None
Mortality	None	None
Adverse Effects		
• Sedation	5%	5%
• Ataxia	Not reported	~20%
• Pruritus	18.9%	1.3%
• Nausea	Not reported	Not reported

Malcolm et al - Conclusions

- “Carbamazepine appeared as effective as lorazepam in decreasing acute symptoms. . .”

Malcolm et al

Strengths

- Assessment with CIWA-Ar
- Inclusion of patients with prior history of alcohol withdrawal seizures and DTs

Malcolm et al - Limitations

- Less severe alcohol impairment:
 - lower average CIWA scores; outpatient treatment; patients were seeking treatment
- Only assessing patients once daily; not indicating timing in relation to medication dose
- Not specifying how taper occurred
- No sample size or power calculation
- Data analysis not determined *a priori*
- Potentially measuring lorazepam withdrawal on day 7
- Possible unblinding of CMZ group due to pruritus

Overall

	Carbamazepine	BZD
CIWA score reduction	✓	✓
Seizures	?	?
DT	?	?
Mortality	?	?
Adverse Effects	Higher rate of pruritus with CMZ Similar rates of ataxia and sedation	

Is there a role for Carbamazepine
in alcohol withdrawal?

Conclusion

☒ Few published trials; small sample sizes

☒ No RCTs evaluating current practice of Symptom Triggered dosing of BZDs vs. Carbamazepine

➔ Not enough evidence to support Carbamazepine over BZDs for the treatment of chronic alcoholics undergoing acute alcohol withdrawal at this time

What Questions Do You Have?

The AMAZING
CARBAMAZEPINE