

Alcohol Abuse a really quick review

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DISCLAIMER

- I have no pertinent financial relationships to disclose.
- Some of the slides in this presentation are from various internet sites and industry sponsored slide sets.
(Forest Pharmaceuticals Inc).

Objectives

- Review the topic of Alcohol Abuse in preparation for the ASAM certification exam, with special attention to...
 - Epidemiological characteristics
 - Medical and behavioral symptoms
 - Pharmacology/acute intoxication
 - Detoxification
 - Pharmacologic and non-pharmacologic Tx
 - Issues related to pregnancy

Since our earliest days, there has been a desire in us to experiment with alcohol

- Genesis 9:20-21 - “And Noah began to be a farmer, and he planted a vineyard. Then, he drank of the wine and was drunk, and became uncovered in his tent.”

Bible

Since our earliest days, there has been a desire in us to experiment with alcohol

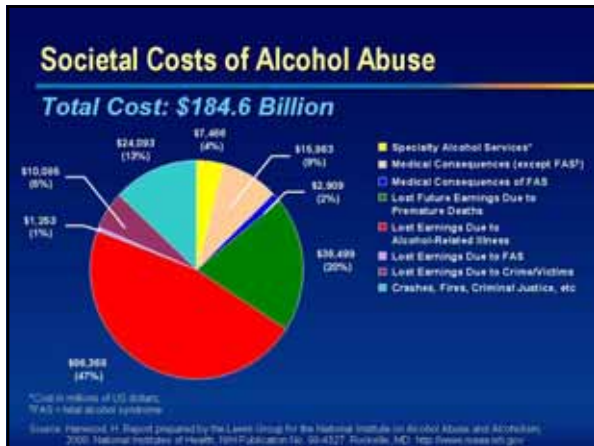
- Genesis 19:33,35,36 - “ So they made their father (Lot) drink wine that night. And the firstborn went in and lay with her father and he did not know when she lay down or when she arose....Then they made their father drink wine that night also. And the younger arose and lay with him and he did not know when she lay down or when she arose. Thus both the daughters of Lot were with child by their father.”

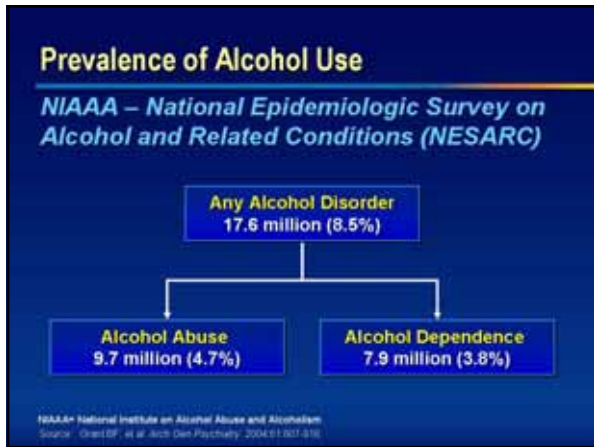
Defining the “Standard Drink”

- A **standard drink** = 14 g ethanol
 - 12 oz of regular beer or cooler (5% alcohol)
 - 5 oz of table wine (12% alcohol)
 - 1.5 oz of hard liquor (40% alcohol, 80 proof)
 - The average person metabolizes about 1 standard drink per hour



Source: National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD 20894, 2004. NIAAA Publication No. 04-3759





- ### National Longitudinal Alcohol Epidemiologic Survey - 1992
- 42,862 face to face interviews, Americans 18 or older.
 - 66% consumed alcohol
 - 49% had first drink before 21
 - 3% had first drink before 14
 - 4.4% alcohol dependent
 - 3% met criteria for alcohol abuse
 - Alcohol use before 14 triples likelihood of being injured while drinking.

Alcohol Abuse

DSM-IV-TR Criteria

Maladaptive pattern of alcohol use leading to clinically significant impairment or distress, manifested within a 12-month period by at least 1 of the following:

1. Failure to fulfill role obligations at work, school, or home
2. Recurrent use in hazardous situations
3. Legal problems related to alcohol
4. Continued use despite alcohol-related social or interpersonal problems

Source: American Psychiatric Association. DSM-IV-TR. American Psychiatric Association, Washington, DC, 2000.

Alcohol Dependence

DSM-IV-TR Criteria

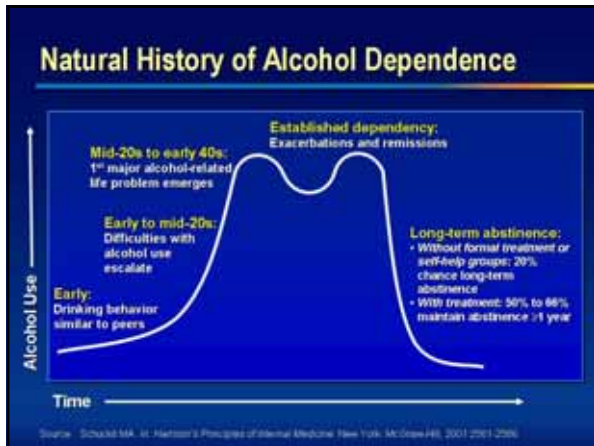
Maladaptive pattern of alcohol use leading to clinically significant impairment or distress, manifested within a 12-month period by at least 3 of the following:

1. Tolerance
2. Withdrawal
3. Loss of control over amount of alcohol consumed
4. Preoccupation with controlling drinking
5. Preoccupation with drinking activities
6. Impairment of social, occupational, or recreational activities
7. Use is continued despite persistent problems related to drinking

Source: American Psychiatric Association. DSM-IV-TR. American Psychiatric Association, Washington, DC, 2000.

Alcohol Dependence

- Type 2 - Begins drinking heavily at an early age (before 12 y/o) - often uses other drugs in combination with alcohol. Experiences medical, legal, and social complications in teens and twenties.
- Type 1 - slower, more "classic" pattern of progression. ~ 75% males alcoholics. Low degree of novelty seeking, fighting, etc.



- ### Systems Affected by Alcohol (partial list)
- **CNS-** "great mimicker" of psychiatric disorders, decreased sleep latency, blackout, peripheral neuropathy Wernike's and Korsakoff's syndromes, cerebellar degeneration, dementia's
 - **GI-** esophagitis, gastritis, enteritis, increased gastric acid production, lowers LES tone, promotes absorption of iron, interferes with absorption of some B vitamins, toxic to pancreas, associated with esophageal, gastric, pancreatic, hepatoma, and colon cancer. Fatty liver, cirrhosis.
 - **Hematopoietic-** pancytopenia, toxic granulocytosis, elevated MCV.

- ### Systems Affected by Alcohol (partial list)
- **Cardiovascular-** increases HDL, 1-2 drinks per day may decrease the risk of cardiac death. decreases myocardial contractility, peripheral vasodilatation- decreases BP in low dose- increases BP long term in high doses, cardiomyopathy, arrhythmias, "holiday heart".
 - **GU-** modest doses increase sex drive- but decrease erectile capacity, testicular atrophy with shrinkage of the seminiferous tubules, amenorrhea, decreased ovarian size, infertility and spontaneous abortions.
 - **Other-** Fetal alcohol syndrome, alcoholic myopathy, osteonecrosis with increased fractures and avascular necrosis of the femoral heads, modest reversible decreases in T3 & T4

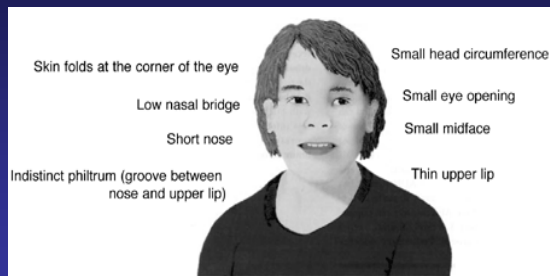
Risk of Drinking During Pregnancy Fetal Alcohol Syndrome (FAS)

- First described in 1968 – syndrome noted in 1:300 to 1:1000 live births in U.S.
- No safe use pattern in pregnancy has been established.
- Some degree of mental retardation noted in 85% of children with FAS
- Hyperactivity, Speech problems, cerebellar dysfunction common later in life.

Fetal Alcohol Syndrome

- Fetal growth retardation in weight, length, and height
- Facial dysmorphism characterized by: short palpebral fissures, hypoplastic maxilla, short upturned nose, flat philtrum, thin upper vermillion border, micrognathia or retrognathia, posteriorly rotated ears, occ. Cleft lip or palate, etc.
- Severe CNS dysfunction: irritability, tremulousness, inconsolable crying, hypertonia, seizures

Fetal Alcohol Syndrome



Source: Warren, K.R. et al.
Alcohol Research & Health
2003;26:1-10

WHY DRINK???

- Prohibition “ the noble experiment” ended in 1933!
- It’s our right!

Solomon wrote in Ecclesiastes 9:15...

“ So I recommend having fun, because there is nothing better for people to do in this world than to eat, drink, and enjoy life...”

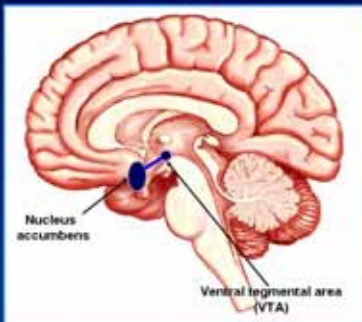
Effects of Acute Alcohol on Reward Circuits

Dopamine and Opioid Systems

- Indirectly increases dopamine levels in the mesocorticolimbic system
 - Associated with positively reinforcing/rewarding effects of alcohol
- Indirect interaction with opioid receptors results in activation of opioid system
 - Associated with reinforcing effects via μ -receptors

Source: Volkow GF, et al. *Neuron*. 2008;59:147-158.
Merrill JC, Jr. *Harrison's Principles of Internal Medicine*. 18th ed. 2007:2681.

Brain Reward Pathways



•The VTA-nucleus accumbens pathway is activated by all drugs of dependence including alcohol

•This pathway is important not only in drug dependence, but also in essential physiological behaviors such as eating, drinking, sleeping, and sex

Source: Merrill JC, Jr. *Harrison's Principles of Internal Medicine*. 2007:2687-2691.

Effects of Acute Alcohol on Other Neural Circuits

GABA and Glutamate Systems

- Increases the effects of GABA, the major inhibitory neurotransmitter in the brain
- Inhibits the effects of glutamate, the major excitatory neurotransmitter in the brain
- Contributes to decreased anxiety and increased sedation during acute alcohol intake

GABA = gamma-aminobutyric acid
Source: Liberson J. Alcohol Health Res World. 1999;22:13-24

Effects of Alcohol on Neural Circuits

Glutamate System



Possible Behaviors with Alcohol Ingestion (non dependant 70kg man)

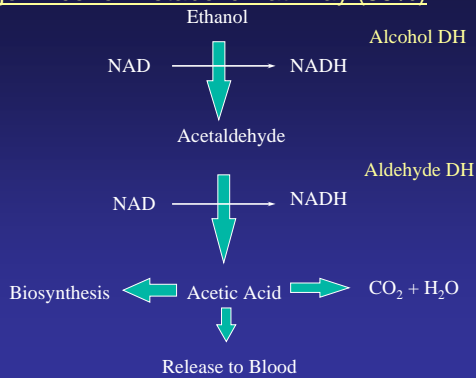
- With .01-.05 g/dL BAC (1 to 2 drinks) -- euphoria and perceived reduction in anxiety
- With .06-.10 g/dL BAC (3 to 5 drinks) -- judgment and motor coordination impaired, sometimes increased aggression
- With 0.20-0.25 g/dL BAC (10 to 13 drinks) -- sedation
- With 0.30- 0.40 g/dL BAC -- memory impairment and loss of consciousness
- With 0.40 to 0.60 g/dL BAC -- depressed respiration , coma, death

Differences in Alcohol Metabolism Between Men and Women

- Women are smaller than men
- Women have lower total body water content (49%) than men (58%) of comparable size
- Gastric ADH lower in women
- Fluctuations in gonadal hormone levels during the menstrual cycle may affect the rate of alcohol metabolism

Alcohol Alerts #10 & #46 - NIAAA

Major Alcohol Metabolic Pathway (85%)



Considerations

- Microsomal ethanol oxidizing system (MEOS – CYP 2E1) also important in first step.
- There are 3 genes that encode hepatic ADH (1-3), with alpha, beta and gamma subunits. ADH sigma - gastric mucosa
- Aldehyde dehydrogenase (ALDH) has 2 types. ALDH 2*1 is most active. ALDH 2*2 is less active, and in ~50% of Chinese and Japanese groups.

Minor Metabolic Pathways

- 10% ethanol can be excreted unchanged in urine, sweat, saliva, and breath.
- 5% of ethanol passing through the liver may be conjugate to inactive ethyl glucuronide (EG).
- EG can be measured in blood, saliva, urine, and hair.

Metabolism Rate (zero order kinetics)

- Relatively fixed- independent of blood concentration
- 80% of adult population- .015 g/dL/hr
- For moderate to heavy drinkers - .017-.020 g/dL/hr

Estimation of BAC

- $BAC = \frac{\# \text{ Drinks} \times 14g/\text{drink}}{\text{Body wt (Kg)} \times FW \text{ (ml/g)} \times 1000g/\text{kg}} \times .806 \times 100\text{mg/dl} - .015\text{g/dl/hr} \times T \text{ (hrs)}$
- FW = Fractional water M= .58 ml/g W= .49 ml/g
- .806g/ml is the constant amount of water per blood volume (80.6%)
- .015 g/dl/hr is the metabolism rate for alcohol (may vary with heavy drinkers)
- Example 5 beers x 14g / 86 kg x .58 ml/g x 1000g/kg = 70g/49,000 ml/kg= .00143
.00143 g/kg x .806 g/ml = .00115 g/ml x 100 ml/dl = .115 g/dl = BAC

Treatment Stages

Stage 1: Identification

Stage 2: Detoxification/Withdrawal

Stage 3: Rehabilitation

Stage 4: Aftercare

Diagnosis- is there a problem ?

- Addiction Severity Index (ASI) – 200 items , 7 subscales – trained interviewer ~1 hour to administer and score. –Free-
- Alcohol Dependence Scale (ADS)- 25 items, 5 minutes to administer- copyrighted-
- Alcohol Use Disorders Identification Test (AUDIT)- 10 item screening questionnaire copyrighted by WHO- Free-
- CAGE- 4 questions asked during history.

AUDIT: Alcohol Use Disorders Identification Test

- 10 items, 4 points each
- Maximum score 40
- Usual cutoff ≥ 8
- Identifies problem (hazardous) drinking and abuse and dependence
- May miss past problems

Alcohol Dependence Screening Tool: AUDIT Questionnaire

1. How often do you have a drink containing alcohol?
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
3. How often do you have 6 or more drinks on 1 occasion?
4. How often during the past year have you found that you were not able to stop drinking once you had started?
5. How often during the past year have you failed to do what was normally expected of you because of drinking?
6. How often during the past year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
7. How often during the past year have you had a feeling of guilt or remorse after drinking?
8. How often during the past year have you been unable to remember what happened the night before because you had been drinking?
9. Have you or has someone else been injured as a result of your drinking?
10. Has a relative, friend, or a doctor or other health care worker been concerned about your drinking or suggested you cut down?

Source: Saunders JB, et al. *Addict*. 1993;88:791-804.

AUDIT score ≥ 8

- Hazardous or harmful drinking
 - Sensitivity 57-95%
 - Specificity 78-96%
- Abuse or dependence
 - Sensitivity 61-96%
 - Specificity 85-96%

Fiellin DA, O'Connor PG. *Ann Intern Med* 2000;133:815-27

CAGE Questions

- Have you ever felt you should Cut down on your drinking?
- Have people Annoyed you by criticizing your drinking?
- Have you ever felt bad or Guilty about your drinking?
- Have you ever taken a drink first thing in the morning (Eye-opener) to steady your nerves or get rid of a hangover?

CAGE

- With two questions answered positively:
- Sensitivity = 60% - 95%
- Specificity = 40% - 95%
- Can miss binge drinkers

Beresford, et al. Lancet 336:482-485

Diagnosis- is there a problem ?

- Drinker Inventory of Consequences (DrInC)- 50 question self administered.
- Michigan Alcohol Screening Test (MAST) 25 item questionnaire- self administered or interview. Also Brief MAST, SMAST, MAST-G, Mm-MAST. – Free-
- Self Administered Alcoholism Screening Test (SAAST)-37 questions- copyrighted

Alcohol Dependence Screening Tool: BMAST Questionnaire

1. Do you feel you are a normal drinker?
2. Do friends or relatives think you are a normal drinker?
3. Have you ever attended a meeting of Alcoholics Anonymous (AA)?
4. Have you ever lost friends or girlfriends/boyfriends because of drinking?
5. Have you ever gotten into trouble at work because of drinking?
6. Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?
7. Have you ever had delirium tremens (DTs), severe shaking, heard voices, or seen things that weren't there after heavy drinking?
8. Have you ever gone to anyone for help about your drinking?
9. Have you ever been in a hospital because of drinking?
10. Have you ever been arrested for drunk driving or driving after drinking?

Source: Finkley RD, et al. Am J Psychiatry. 1972;129:542-545.

Possible LAB Findings

- **Gamma-glutamyl Transpeptidase (GGT)**- most widely used, accurate marker for heavy alcohol consumption-production may be stimulated by alcohol, and cell damage may cause leakage. Also elevated in steatohepatitis and biliary tract disease
- **Aspartate Aminotransferase (AST)**- increased in liver damage associated with alcohol intake, but not very sensitive or specific.
- **Mean Corpuscular Volume (MCV)**- increased as a direct result of the toxic effect of alcohol, but can be elevated by many other causes. More specific when used with GGT in absence of cirrhosis.

Possible LAB Findings

- **Carbohydrate-deficient Transferrin (CDT)**-chronic alcohol consumption decreases the number of carbohydrate moieties (galactose, N-acetylglucosamine, sialic acid, mannose, etc.) attached to transferrin. Effect most evident at >3 drinks per day.
- Marker combinations are more sensitive and specific (CDT+ GGT), (GGT+MCV)
- Ethyl Glucuronide is not a marker, but a direct measure of an alcohol metabolite. This test is becoming more readily available.
- Combination of lab findings and clinic hx is best.

Detox- yes, no, maybe?

- Detoxification implies safely separating the patient from the toxic effect of the drug.
- It may or may not require pharmaceutical assistance.
- The goal is to prevent harmful sequelae (such as withdrawal seizures, Delirium Tremens, acute psychotic episodes, and irrational dangerous behaviors).

CIWA-Ar

- Clinical Institute Withdrawal Assessment - revised version (CIWA-Ar)
 - Structured Severity Assessment Scale
 - Objective Scale for use by health care personnel to evaluate patients at risk for developing alcohol withdrawal syndromes, and quantify the severity of withdrawal.
- “Detox language”- to relate severity of symptoms to clinic and non-clinical reviewers.

Clinical Institute Withdrawal Assessment for Alcohol Scale-revised (CIWA-Ar)

- 10 item rating system for alcohol withdrawal severity max of 67 points:
 - 0- no symptoms
 - 1- Mild
 - 4- Moderate
 - 7- Severe
- BP and HR not found to correlate with severity of withdrawal
- Can be given in under 2 minutes

Sullivan, J.T. British Journal of Addiction, 1989; 84: 1353-7.

Clinical Institute Withdrawal Assessment for Alcohol Scale-revised (CIWA-Ar)

- | | |
|------------------------|------------------------------|
| 1. Nausea and vomiting | 6. Tactile disturbances |
| 2. Tremor | 7. Visual disturbances |
| 3. Paroxysmal sweating | 8. Auditory disturbances |
| 4. Anxiety | 9. Headache or fullness |
| 5. Agitation | 10. Orientation (0-4 points) |

Sullivan, J.T. British Journal of Addiction, 1989; 84: 1353-7.

Which Detox Method is Best?

- Working Group from ASAM published an evidence based practice guideline on Pharmacological Management of Alcohol Withdrawal-
JAMA July 9, 1997.
- Meta-analysis reviewing 134 articles including 65 prospective controlled trials involving 42 medications.

Outcomes Reviewed

1. Severity of withdrawal syndrome
2. Alcohol Withdrawal Delirium
3. Withdrawal Seizures
4. Completion of withdrawal
5. Entry into Rehab
6. Cost

Benzodiazepines

- Reduction of alcohol withdrawal symptoms in six prospective trials with:
 - Chlordiazepoxide
 - Diazepam
 - Lorazepam
- Overall reduction of seizures (7.7 per 100 treated)
- Reduction of delirium tremens (4.9 per 100 treated)
- All were equally efficacious*

Mayo-Smith, M et al. Pharmacological Management of Alcohol Withdrawal. JAMA. 1997;278: 144-51.

Results

- Treatment should be individualized.
- Benzodiazepines work best for moderate to severe withdrawal.
- Carbamazepine may also be useful.
- Neuroleptics may decrease delirium in combination with benzo's but are less effective as mono-therapy and may lower seizure threshold.
- Thiamine administration on admission may prevent Wernicke-Korsakoff's in high risk pt
- B-blockers, Clonidine, Mg **generally** not helpful.

My Personal Advice

- Be sure your staff is able and willing to use the CIWA-Ar in timely and correct fashion if you are going to use a purely "symptom triggered" protocol with short acting benzodiazepines.

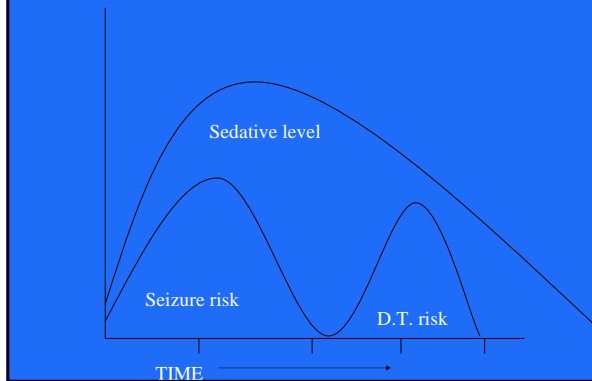
Sample Detox Protocols

- Diazepam 10mg every 4 hours while awake x 24h +/- lorazepam prn (>10), then QID x 24h prn, then 5mg QIDx24h prn, then 2mg QID prn x24h then d/c.
- Lorazepam 2mg -repeat in 1 hr for CIWA-Ar >8, then give every 4 hours prn (>8) x 48h, then decrease to 1mg every 4h prn.

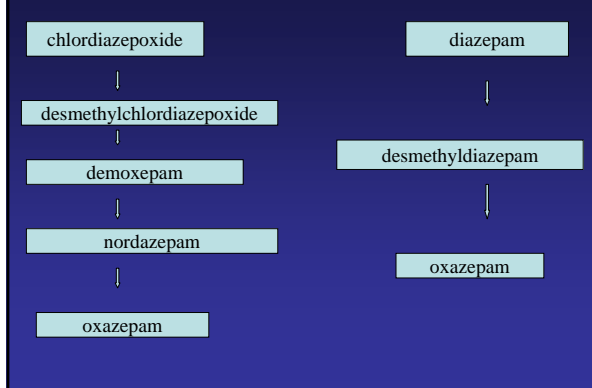
Sample Detox Protocols

- Carbamazepine- 200mg QID on day one, then 200mg TID day 2, then BID, then QD.
- Chlordiazepoxide 50mg QID while awake on day one, the 50mg TID prn on day 2, then 25mg prn day 3-4 (>8).

Sedative Detoxification (front-loading technique)



Metabolism of Selected Benzodiazepines



Contraindications to long-acting sedative use for detoxification

- Medically unstable patients.
- Patients with decompensated liver disease (acute or chronic).
- Unexplained delirium.
- Respiratory compromise.



Consider use of lorazepam which is conjugated to the inactive glucuronide.

Detoxification During Pregnancy

- Benzodiazapines, barbiturates, and carbamazapine all have potential fetal toxicities. Benzo's are the treatment of choice -dosed to relieve signs& symptoms.
- They are all significantly less teratogenic than alcohol.
- Detox should be performed in an inpatient setting with OB/GYN consultation.

Treatment Stage 3: Rehabilitation

Goals:

- Enhance function
- Optimize motivation toward complete abstinence
—via motivational interviewing
- Restructure life without alcohol
- Relapse prevention

Naltrexone

- VA study Dec 13, 2001 NEJM
- 627 veterans given 12 mo Naltrexone, or 3 mo. Naltrexone and 9 mo placebo, or 12 mo placebo
- No statistically significant difference in # days to relapse at 13 weeks, and no difference in % days drinking at 52 weeks

Krystal, et al. NEJM Volume 345, pg. 1734-39, Dec 13, 2001

Campral® Pharmacodynamics

- Unique mechanism of action in maintaining abstinence is not completely understood
- Chronic alcohol exposure is thought to alter normal balance between neuronal excitation and inhibition
- Campral is believed to act on the biochemical systems that are involved in alcohol dependence
 - *In vitro* and *in vivo* studies in animals suggest acamprosate may interact with glutamate and GABA neurotransmitter systems to restore balance

Campral is a registered trademark of Merck-Sandoz.
Source: Campral Prescribing Information - Forest Pharmaceuticals, Inc.

Pharmacokinetics (cont)

Special Populations

- No pharmacokinetic differences due to gender
- No pharmacokinetic differences in alcohol-dependent subjects
- No dose adjustment necessary with mild to moderate hepatic impairment or mild renal disease
- Dose adjustment is necessary in moderate renal disease (ie, creatinine clearance, 30-50 mL/min)
- Contraindicated in severe renal disease (ie, creatinine clearance, ≤ 30 mL/min)

Campral is a registered trademark of Merck-Sandoz.
Source: Campral Prescribing Information - Forest Pharmaceuticals, Inc.

Drug Interactions

- No inducing potential on cytochrome CYP1A2 and 3A4 systems
- Does not inhibit metabolism mediated by cytochrome CYP1A2, 2C9, 2D6, 2E1, or 3A4
- No pharmacokinetic interaction with alcohol, disulfiram, or diazepam
- No dose adjustment needed with naltrexone
- Can be taken with anxiolytics, hypnotics, and sedatives (including benzodiazepines) or nonopioid analgesics

Campral is a registered trademark of Merck Serono
Source: Campral Prescribing Information, Forest Pharmaceuticals, Inc.

Acamprosate Double-Blind, Placebo-Controlled Pivotal Clinical Trials

Reference	Treatment Groups	Key Findings
Pelc II, 1997 (France/Belgium) 13-week study	Placebo (n=62) ACAMP, 1998 mg/d (n=63)	• ACAMP > Placebo for complete abstinence, % days abstinent, CAD, and time to first drink • Differences statistically significant
Sass, 1996 (Germany) 48-week study	Placebo (n=136) ACAMP, 1332 and 1998* mg/d (n=136)	• ACAMP > Placebo for complete abstinence, % days abstinent, and time to first drink • Differences statistically significant
Paille, 1995 (France) 52-week study	Placebo (n=177) ACAMP, 1998 mg/d (n=173)	• ACAMP > Placebo for complete abstinence, % days abstinent, and time to first drink • Differences statistically significant

*ACAMP = acamprosate; CAD = cumulative abstinence duration.
*Individual dosage based on body weight: 480 mg, 1080 mg, or 1332 mg/d.
Source: Pelc I, et al. *Br J Psychiatry*. 1997;171:73-77.
Sass H, et al. *Arch Gen Psychiatry*. 1996;53:673-680.
Paille P, et al. *Alcohol Alcohol*. 1995;30:233-241.

Complete Abstinence: Original Study vs FDA Reanalysis

Study		Acamprosate 1998 mg/d	Placebo	P-value
Pelc II, 1997 13-week study	Original Study	41%	15%	<.001
	FDA Reanalysis	38%	13%	.001
Sass, 1996 48-week study	Original Study	45%	25%	.005
	FDA Reanalysis	28%	13%	.002
Paille, 1995 52-week study	Original Study	19%	11%	NS* (.096)
	FDA Reanalysis	18%	9%	.044

*NS=Not Significant
Source: Pelc I, et al. *Br J Psychiatry*. 1997;171:73-77.
Sass H, et al. *Arch Gen Psychiatry*. 1996;53:673-680.
Paille P, et al. *Alcohol Alcohol*. 1995;30:233-241.
Data of the Forest Laboratories, Inc.

Non-Pharmacologic Treatment

- 12 Step meetings- AA/ Celebrate Recovery
- Insight oriented “process” groups
- Cognitive Behavioral Therapy
- Motivational Enhancement
- Coping Skill Enhancement

- No group has a significantly better outcome than the others- given the same length of treatment.

Alcoholics Anonymous

- Over 2,000,000 “members” world wide.
- Ubiquitous- >97,000 groups world wide.
“friends of Bill W.”
- 39% of members were referred by health care professional.
- www.aa.org

Celebrate Recovery

- 12 Step group- claiming Jesus Christ as the higher power.
- 4500 groups in 48 states, 22 state prison systems, and 12 countries.
- “Umbrella program” for all chemical dependencies, co-dependency, compulsive behaviors, abuse, pre-recovery
- www.celebraterecovery.com

Questions & Discussion