

## Varenicline:

A new CHAMPION for alcohol dependence?  
OR  
Should we have high spirits?

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28 Feb 2013

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## DSM IV Criteria

A maladaptive pattern of drinking, leading to clinically significant impairment or distress, as manifested by at least one of the following occurring within a 12-month period:

**Abuse:**

- Recurrent use of alcohol
  - failure in major obligations
  - use when physically hazardous
  - legal problems
  - despite social/interpersonal problems
- Does not meet definition of dependence

**Dependence:**

- ↓ effect of alcohol
- Physical withdrawal symptoms
- Drinking in larger amounts or over a longer period than intended
- Persistent desire and failure control drinking
- Activities affected by drinking
- Great deal of time recovering from drinking
- Continued drinking despite knowledge of problems caused or exacerbated by drinking.

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## Alcohol Misuse in Canada

**Social Costs**

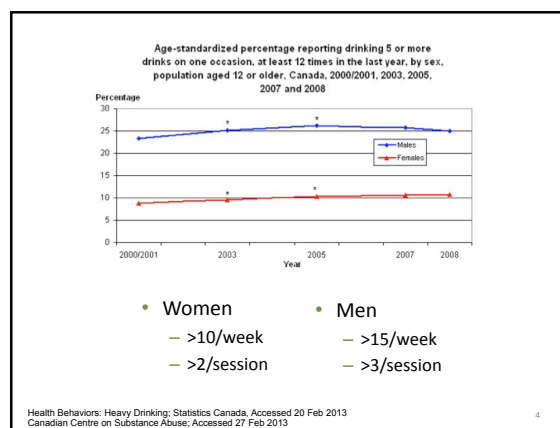
- Consequences to Health/welfare system
- Decreased productivity
- Crime / law enforcement
- Road accidents
- Fires
- Environmental
- Research and prevention
- Loss of life
- Pain and Suffering

**Selected Alcohol WHO Drug-attributable diseases**

- Low birth weight
- \*Cancers (liver, breast, mouth)
- \*DM
- Depressive disorders
- Epilepsy
- \*HTN
- \*Cerebrovascular disease
- Cirrhosis
- Falls
- Drowning

International Guidelines for the Estimation of the Avoidable Costs of Substance Abuse, Health Canada, Accessed 20 Feb 2013

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## Alcohol Dependence and Abuse Tx

**Non-Pharmacological**

- Counseling
  - ↓consumption 4 drinks/week
- Abstinence programs
  - ⊖
- Managed Alcohol Programs
  - ⊖

**Pharmacological**

- Disulfiram ⊖
- Naltrexone NNT=8
- Acamprostate NNT=5
- Topiramate
- Baclofen
- SSRI's
- Ondansetron

\*Cochrane Collaboration

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## Varenicline

- Indication:
  - smoking-cessation
- Adverse Effects
  - GI (N/V/C/F/metallic taste)
  - Neurologic (vivid dreams, insomnia, headache)
  - Black Box Warning: Psychiatric disorder
- ?Decrease alcohol consumption

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## Clinical Question

- P** Patients with a history of heavy drinking/  
alcohol dependence/abuse
- I** Varenicline
- C** Standard of Care / Placebo
- O** Decrease alcohol consumption  
Eliminate S/Sx of dependence  
Abstinence  
Improve QOL  
Decrease morbidity / mortality

## Search Strategy

<b>DATABASES</b>	PubMed, Embase, Google, Google Scholar, IPA, Cochrane, Clinicaltrials.gov
<b>SEARCH</b>	Varenicline, Ethanol, Alcohol abuse, Alcoholism
<b>LIMITS</b>	Human
<b>RESULTS</b>	6 RCT (3 unpublished) 1 Observational (recovering dependence) 2 Review 2 Case Report 1 Cochrane Protocol

## Measuring Tools

- Alcohol Urge Questionnaire (8 items)
  - desire to drink
  - expectation of +ve effects
  - inability to avoid if alcohol available
  - Max score 56
- Obsessive Compulsive Drinking Scale (14 items)
  - Compulsion sub-scale
  - Obsession sub-scale
  - Max score 40
- Used to monitor over treatment duration (trend)

## Subjective Response to Alcohol

- 0 - 36 VAS
- Subjective assessment of “drug effect” and “intoxication”
- Developed in sons of alcoholics and control match pairs (n=46)

## Varenicline Reduces Alcohol Self-Administration in Heavy-Drinking Smokers

Sherry A. McKee, Emily L.R. Harrison, Stephanie S. O'Malley, Suchitra Krishnan-Sarin, Julia Shi, Jeanette M. Tetraault, Marina R. Picciotto, Ismene L. Petrakis, Naralys Estevez, and Erika Balchunas  
BIOL PSYCHIATRY 2009;66:185–190

## McKee et al. 2009

- P** Non-alcohol-dependent heavy drinking smokers
- I** Varenicline 2mg/day (n=10)
- C** Placebo (n=10)
- O** Smoking behavior  
Number of drinks consumed  
Alcohol craving

### Methods

- R DB PC
- 7 day run in period for varenicline titration
- “Priming drink” 0.3g/kg (~2.3 oz for 70kg)
  - Subjective measures
- EtOH self administration at 50 and 120min
  - Could choose either:
    - Up 4 drinks (0.15mg/kg each) or
    - \$3/non-consumed drink

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### McKee et al. 2009

**Inclusion**

- ≥21 years old
- ≥10 cigarettes/day
- Alcohol consumption
  - Women
    - >7/week
    - >3/session
  - Men
    - >14/week
    - >4/session

**Exclusion**

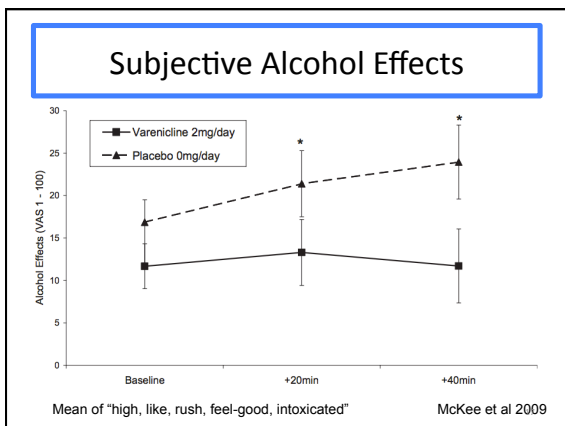
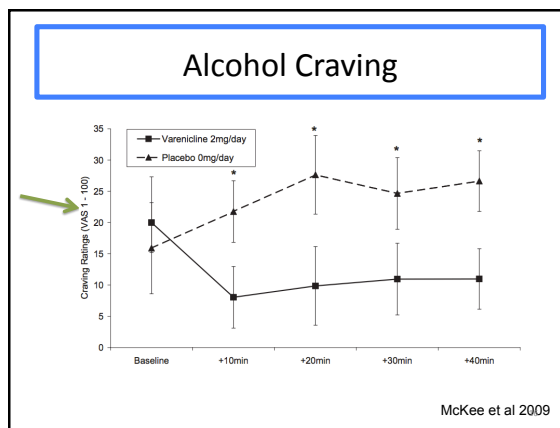
- Alcohol dependence
- Illicit drug use (cannabis OK)
- Psychoactive drug use
- Pregnant/nursing
- Contraindicated to EtOH consumption
  - ie LFT >3x ULN
- Varenicline allergy

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### Baseline

- 80% male
- 35 yrs old
- 1 Pack per day smokers
- Drinking mean 4 days/week
- Consuming 7 drinks/session

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### Results

	Varenicline (n=10)	Placebo (n=10)	P-value
Pre-treatment Alcohol frequency	-1.54 days	-0.01 days	0.07
Adverse Effects	3	4	X
Cigarettes smoked during 3 smoke breaks (2:40)	3.78	5.39	<0.05
Physiologic measures HR, BP, Skin temp	NSS		X
Drinks consumed	0.5	2.6	<0.05
Number abstinent	8	3	<0.03 <sub>18</sub>

## Conclusions

- Decreased “self administration”
- Absolute Number Drinks Reduction
  - Varenicline: -6.5 drinks per session
  - Placebo: -3.4 drinks per session

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## Critique

- Did not define “alcohol dependence”
  - Patients excluded if alcohol dependent
  - DSM-IV?
- Referenced AUQ but reported a VAS 1-100
- Referenced Subjective Alcohol Effects but reported VAS 1-100
- >ADE in placebo group
- Controlled “Lab-Bar” setting

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## A preliminary investigation of varenicline for heavy drinking smokers

Lisa M. Fucito · Benjamin A. Toll · Ran Wu ·  
Denise M. Romano · Ece Tek · Stephanie S. O'Malley

Psychopharmacology (2011) 215:655–663

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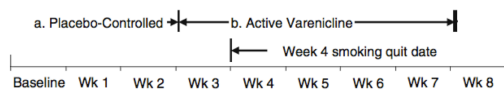
## Fucito et al. 2011

- P Heavy drinking smoker
- I Varenicline 2mg/day x8 weeks (n=15)
- C Placebo x3 weeks then, titration x1 week, Varenicline 2mg/day x4 weeks (n=15)
- O Pre-treatment: % heavy drinking days  
Post-Quit day: % heavy drinking days, abstinence from smoking

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## Methods

- R DB PC → Open label
- Pretreatment:
  - Varenicline titrate to 2mg/day x3weeks
  - Placebo x3 weeks then titrate to 2mg/day
  - Discussed smoking cessation weeks 1-4
  - Discussed decreased ETOH consumption week 4
- Open label post-quit date
  - Varenicline 2mg/day x4 weeks



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## Fucito et al. 2011

### Inclusion

- 18-75years old
- **≥5 cigarettes ≥3 days/week**
- Alcohol consumption exceeded every week (past 4 weeks)
  - Women
    - >7/week
    - >3/session
  - Men
    - >14/week
    - >4/session

### Exclusion

- Serious illness
- Current drug dependence besides nicotine
- **Physical Alcohol withdrawal**
  - Hx seizures, delirium, hallucinations during withdrawal
- Illicit drug use
- **Use of clonidine, bupropion, nortriptyline**
- Other tobacco products

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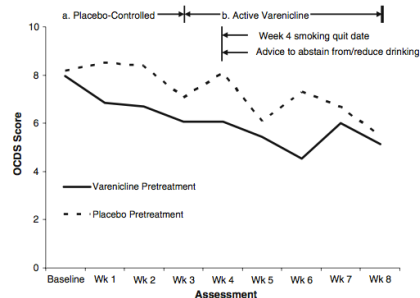
## Baseline

- 40 years old
- 53% male
- 90% caucasian
- 1 PPD
- 80% alcohol dependant

	Varenicline	Placebo
% heavy drinking days	42.67 ± 26.28	48.44 ± 31.99
OCDS	7.95 ± 3.71	8.16 ± 3.42

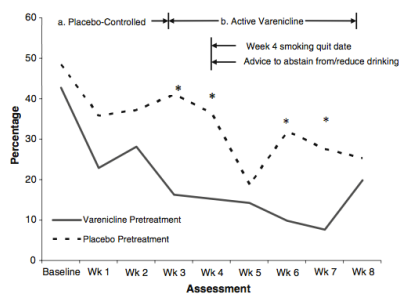
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## Results: Alcohol Cravings



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## Results: % heavy drinking days



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## Authors' Conclusions

- "...reported significantly greater reductions in alcohol craving
- numerically fewer heavy drinking days compared to those who received placebo
- these differences persisted during the open-label phase"

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## Conclusion

- Both groups got to same place
- Heavy drinking days rebounded
- ?Efficacy in Alcohol Dependant Patients
- Absolute decrease cravings:
  - 2 points OCDS
- Absolute decrease % heavy drinking days:
  - Varenicline 25%
  - Placebo 20%

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## Critique

- Decrease in alcohol consumption and cravings previously linked to decreased smoking
- 8 weeks total, lack of further follow-up
  - ?rebound in consumption?
- Heavy drinker seeking smoking cessation

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## Varenicline decreases alcohol consumption in heavy-drinking smokers

Jennifer M. Mitchell • Candice H. Teague •  
Andrew S. Kayser • Selena E. Bartlett •  
Howard L. Fields

Psychopharmacology (2012) 223:299–306

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## Mitchell et al. 2012

**P** Non-treatment seeking heavy drinking smokers

**I** Varenicline 2mg/day x12 weeks (n=29 or 33)

**C** Placebo (n=31 or 35)

**O** -# alcoholic drinks/week -Cumulative cigarettes/  
-Cigarettes/week alcoholic drinks  
-Alcohol craving/week -# abstinent days

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## Methods

- R DB PC
- Recruited social drinkers from Craigslist
  - Non-treatment-seeking heavy drinkers
- 12 weeks of treatment
  - Titration on and off drug
- Quit one week into study
- Used computerized diaries for cigarette/alcohol consumption
- Assessed compliance with special bottle caps and riboflavin

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## Mitchell et al. 2012

### Inclusion

- ≥21 years old
- ≥10 cigarettes/day
- Alcohol consumption
  - Women
    - >7/week
  - Men
    - >14/week

### Exclusion

- Alcohol dependence / abuse
- Psychiatric comorbidities
- Previous treatment
- ≤2/week illicit drug use
- Pregnancy

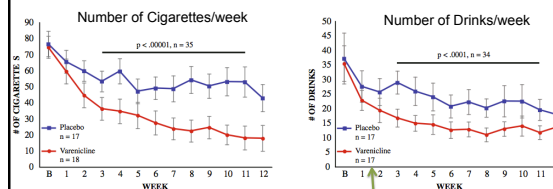
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## Baseline

	Placebo	Varenicline
Age (median)	25	29
Male	55%	55%
Mean # Drinks per week (range)	37 (5-144)	35 (3-105)
Mean # Cigarettes per week	77	75
OCDs	12.0	11.0

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## Results



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### Results

- Alcohol craving “trended” towards varenicline
  - NSS
- No difference in # abstinence days
- No correlation between change in drinking and change in smoking
- Compliance caps: 88%

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### Adverse Effects

- Side effects similar in both groups at baseline at 12 weeks
- Five severe adverse events reported

Varenicline	Placebo
Anger, aggression, vivid nightmares	Suicidal thinking
Nausea / vomiting	
Headache and nausea	
Anger agitation, sleep disturbance	

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### Conclusions

- No affect on abstinence
- Decrease in total drinks
  - Patients would start drinking, but consume fewer drinks
- ?Use in patients attempting to cut down?

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### Critique

- Alcohol dependant excluded
- Half dropped out (34 PP vs 64 ITT)
- Did not tell us who dropped out (which arm)
  - “similar” for both arms
  - Report total numbers
- Still unclear if decrease in drinks is due to drug or due to decrease in cigarettes
- Collected data up to 16 weeks follow-up but report 12 weeks

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### Clinical Question

Patients experiencing alcohol abuse or dependence		X
Heavy drinking smokers	✓	
Alcohol dependant smokers	✓	
Decrease total number of alcoholic drinks	✓	-3.5/day
Decrease alcohol craving	✓	OCDS -2 pts
Decrease “positive” alcohol effects	✓	-8 pts
Increase abstinence	X(ish)	
Improve QOL	X	
Decrease morbidity / mortality	X	

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### Next steps

- Trials with non-smoking drinkers
  - 2 ongoing/recruiting
  - 1 Cochrane Protocol
- Other potential applications:
  - Methamphetamine Abuse
  - Cocaine Abuse
  - Parkinson Disease

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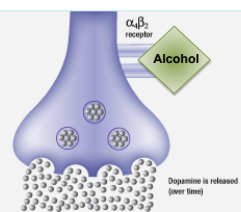
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8. Mitchell JM, Teague CH, Kayser AS, Bartlett SE, Fields HL. Varenicline decreases alcohol consumption in heavy-drinking smokers. *Psychopharmacology (Berl)*. 2012;223:299-306.
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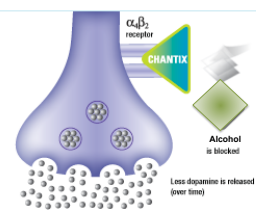
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## MOA

### NICOTINE—AGONIST ACTION



### CHANTIX—AGONIST AND ANTAGONIST ACTIONS



[www.pfizerpro.com](http://www.pfizerpro.com) accessed 7Feb2013

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