



ADDICTION MEDICATIONS

NEW YORK STATE OFFICE OF ALCOHOLISM AND SUBSTANCE ABUSE SERVICES

Workbook prepared by the Office of the Medical Director
and the Bureau of Treatment:

- Steven Kipnis MD, FACP, FASAM
- Robert Killar, CASAC
- Patricia Lincourt, LCSW



- The Associated Press reported April 3, 2006 that Nora Volkow, director of the National Institute of Drug Abuse (NIDA) said that adolescent brains are still developing and react differently to drugs than those of adults. Volkow, a researcher with a long history of exploring the brain circuitry involved in addiction, has been shifting some of NIDA's research efforts toward examining how the brains of adolescents and people who don't become addicted to alcohol or other drugs differ from the brains of those who do develop drug problems. "What is it that makes a person more vulnerable to take drugs or not?" said Volkow.
- "Now we have Nora's picture rather than a picture of fried eggs," said Joanna Fowler, a former colleague of Volkow's at the Brookhaven National Laboratory. "We can go beyond that knee-jerk picture of a brain to a real brain ... **If you can conceptualize (addiction) as a brain disease rather than a moral weakness or lack of willpower, you can more easily bring resources to bear.**"



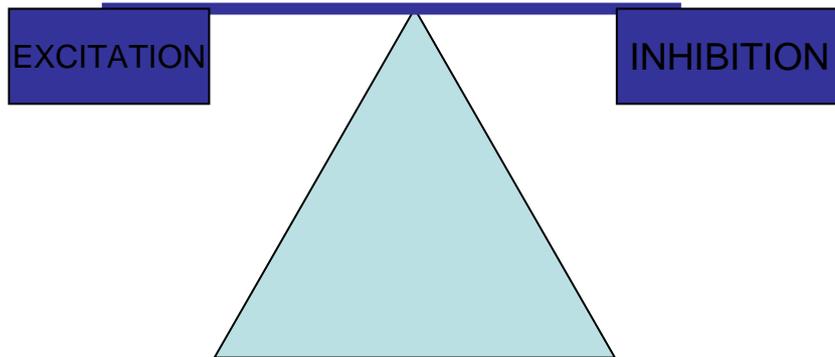


ACAMPROSATE

- Calcium acetyl homotaurinate (Campral®)
- Available 1/2005
 - Delayed release tablets
 - Daily dose is two 333mg tabs three times a day (TID)
- Enhances abstinence and reduces drinking days
- A very important factor is that it is not metabolized in the liver



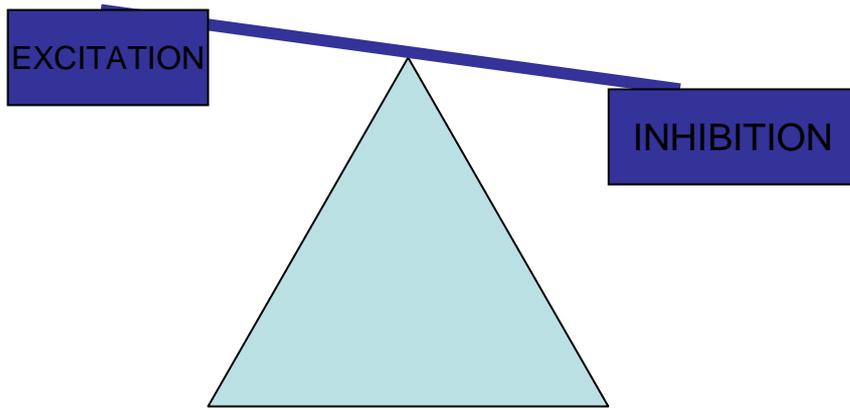
ACAMPROSATE – HOW DOES IT WORK?



There is a baseline equilibrium in the brain between excitatory neurotransmitters (glutamate and aspartate) and inhibitory neurotransmitters (gaba and taurine).



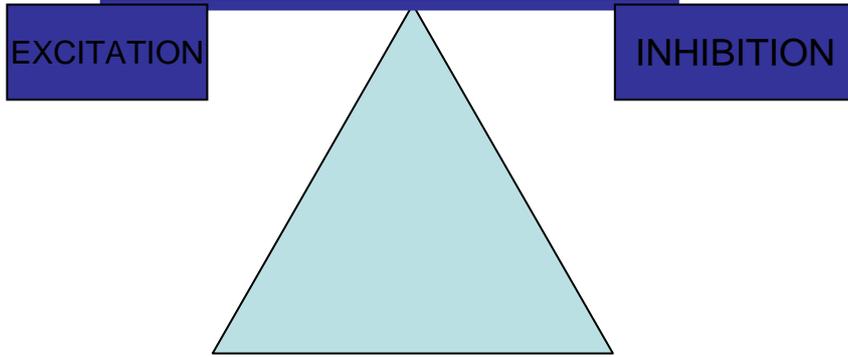
ACAMPROSATE



When there is acute alcohol intake, the effect is to decrease glutamate, thus inhibition increases (stronger effect due to the sedative nature of alcohol)



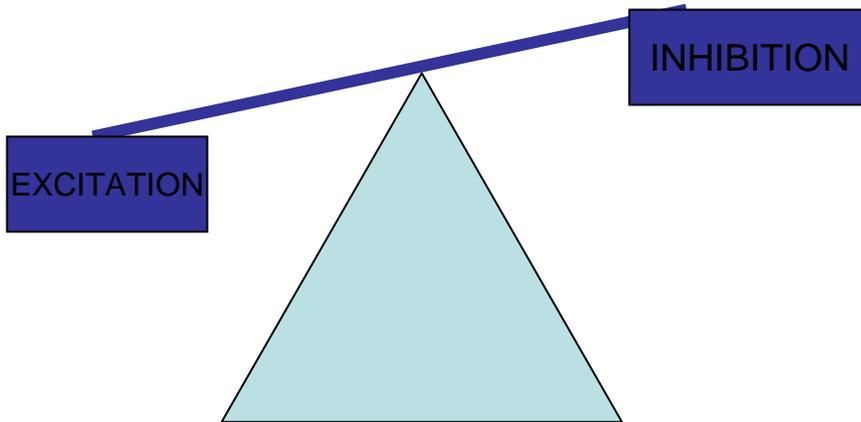
ACAMPROSATE



In chronic alcohol use, one sees neuroadaptation whereby there is up-regulation of the NMDA receptor. This up-regulation is manifested by an increase in the number of receptors and an overall balance in the brain.



ACAMPROSATE



When the alcohol dependent patient stops drinking and goes into alcohol withdrawal, the brain picture is one of imbalance where there is an increase in glutamate (excitation is dominant). This results in hyperactivity (seizures, etc). Repeated withdrawal increases glutamate significantly.



ACAMPROSATE

- Acamprosate has a binding site on glutamate receptors, glutamate being an excitatory neurotransmitter. When alcohol consumption is stopped, there is a **hyper - excitable state** that is at least partially due to the glutamate system.
 - **Inhibits glutamate's release, thus decreasing the degree of excitation or withdrawal.**



ACAMPROSATE

- Acamprosate may restore receptor tone that usually can take up to 12 months to normalize on its own.
- Thus, there is attenuation of the symptoms of acute and protracted alcohol withdrawal.



ACAMPROSATE

- Well tolerated with major side-effect being intestinal cramps and diarrhea
- Not metabolized by the liver and is eliminated 90% unchanged in the urine
- There have been no significant drug - drug interactions reported
- Dosing was 2000mg divided into twice day dosing in the European studies, which is different than the suggested US prescribing guidelines



ACAMPROSATE

- Whitworth and colleagues showed a relapse rate of 19% in a 12 week study period (23% with Revia).
 - Patients stated that they “seemed to lose interest in alcohol”
 - European studies involving over 4000 subjects had good results in 11 out of 12 studies, though the drop out rate was high (~50%)



ACAMPROSATE

- In another study, abstinence was 38% at 13 weeks compared to 13% of placebo patients.
 - 28% vs 13% at 48 wks
 - 16% vs 9% at 52 wks
- Improved time to first drink (140 days vs 40 days in 48 week trial)
- Improved % days abstinent (70% vs 30%)

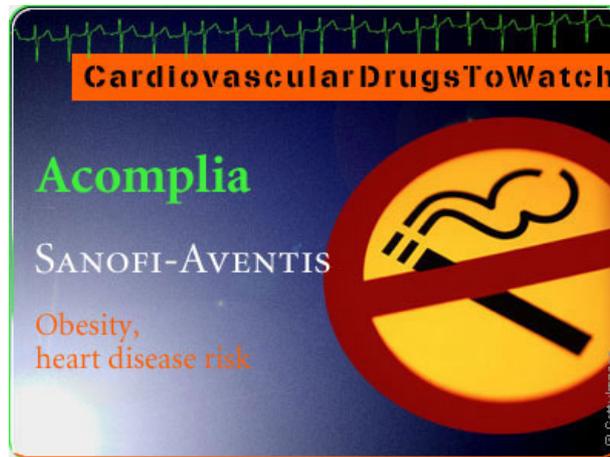


ACAMPROSATE

- University of Lausanne, Switzerland showed **increase effectiveness if acamprostate was combined with antabuse** and no adverse drug interactions were noted
 - NOTE: the combination of medications has not been shown to be as effective if one goes by the COMBINE study in the US.



ACOMPLIA (RIMONOBANT)



- Initial trials for the treatment of:
 - Obesity
 - Nicotine Dependence
 - Alcohol Dependence
 - Marijuana Dependence
- Probable FDA approval for obesity, other uses would be off label.



ACOMPLIA

- Rimonabant manufactured by Sanofi-Aventis
- Works through the endocannabinoid system and its effect on the reward system
 - Chronic smoking and eating overactivate the endocannabinoid system
 - Rimonabant blocks the effect of endocannabinoids by preventing their attachment to the brain cells they normally stimulate

OR



ACOMPLIA

- Rimonabant acts as an inverse agonist, where the opposite of the expected result is seen when the medication binds to the receptor.
 - THC, the main psychoactive chemical in marijuana, causes increased appetite
 - Rimonabant with full stimulation causes decreased appetite = inverse agonist effect





TOPIRAMATE

- Topiramate (Topamax®)
 - Originally synthesized as anti-diabetic agent
 - Approved for partial onset and primary generalized tonic-clonic seizures in adults and children



TOPIRAMATE

- Topiramate (Topamax®)
 - 1/2 life 19-23 hours
 - 50-80% excreted unchanged in the urine
 - No therapeutic range is suggested
 - Blood level monitoring is not indicated



TOPIRAMATE

- Topiramate (Topamax®) adverse effects
 - Transient paresthesias (numbness and tingling in the arms, legs, hands and feet)
 - Decrease cognition (decrease in concentration and memory)
 - Secondary angle closure glaucoma – rare
 - Kidney stones (1.5% or 2-4 times the general population)
 - Weight loss



TOPIRAMATE

- Topiramate (Topamax®) medication interactions:
 - Decreases estrogen effect of birth control pills
 - Increased Haldol blood level seen with concurrent use
 - Tegretol and Dilantin will decrease topiramate levels

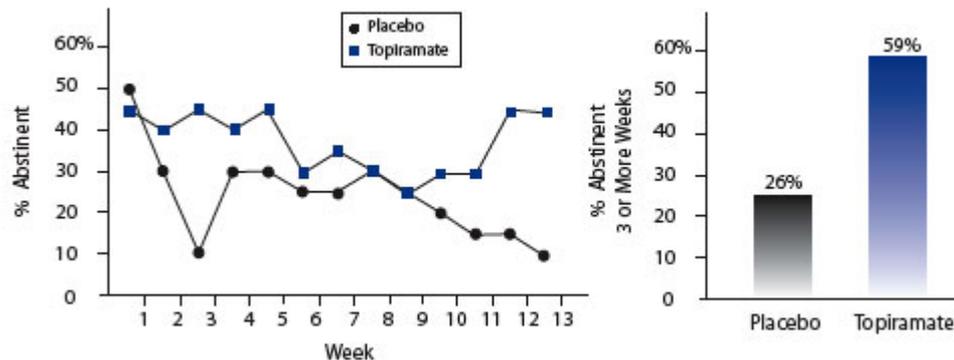


TOPIRAMATE

- Topiramate (Topamax®)
 - Found to be more effective than controls and reduced the number of heavy drinking days.
 - No difference in early or late onset alcoholics
 - Study measured abstinence initiation not persistence
 - Perhaps different pharmacotherapies could be used for initiation, maintenance and prolonged abstinence
 - Work by B.Johnson in Lancet 2003;361;1677-1685.



TOPIRAMATE



- Topiramate (Topamax®)
 - Effect on cocaine users
 - 25mg to start, increase by 25 mg daily dose/week until 200mg per day is reached
 - In almost every week of the study, more patients were abstinent in the topiramate group than in the placebo group. Of the 40 participants in the study, more patients taking topiramate achieved 3 or more continuous weeks of abstinence from cocaine.

(Kampman, K.M., et al. A pilot trial of topiramate for the treatment of cocaine dependence. Drug and Alcohol Dependence 75(3):233-240, 2004.)



Use of Oral Topiramate to Promote Smoking Abstinence Among Alcohol-Dependent Smokers

A Randomized Controlled Trial

- **ABSTRACT**

- **Background** Previously, our group has shown that topiramate is an effective treatment for alcohol dependence. Herein, we extend that proof-of-concept study by determining whether cigarette-smoking, alcohol-dependent individuals from the earlier study also experienced improved smoking outcomes.
- **Methods** As a subgroup analysis of a larger double-blind, randomized, controlled, 12-week study comparing topiramate vs placebo as treatment for alcohol dependence, a 12-week clinical trial compared topiramate vs placebo in 94 cigarette-smoking, alcohol-dependent individuals. Of these, 45 were assigned to receive topiramate (escalating dose from 25 to 300 mg/d) and the remaining 49 had placebo as an adjunct to weekly standardized medication compliance management. The primary outcome was smoking cessation ascertained by self-report and confirmed by the level of serum cotinine (nicotine's major metabolite).



Use of Oral Topiramate to Promote Smoking Abstinence Among Alcohol-Dependent Smokers

A Randomized Controlled Trial

- **ABSTRACT (Continued)**
 - **Results** Topiramate recipients were significantly more likely than placebo recipients to abstain from smoking (odds ratio, 4.46; 95% confidence interval, 1.08-18.39; $P = .04$). Using a serum cotinine level of 28 ng/mL or lower to segregate nonsmokers from smokers, we found that the topiramate group had 4.97 times the odds of being nonsmokers (95% confidence interval, 1.1-23.4; $P = .04$). Smoking cessation rates for topiramate recipients were 19.4% and 16.7% at weeks 9 and 12, respectively, compared with 6.9% at both time points for placebo recipients.
 - **Conclusion** In this trial, topiramate (up to 300 mg/d) showed potential as a safe and promising medication for the treatment of cigarette smoking in alcohol-dependent individuals.

Bankole A. Johnson, DSc, MD, PhD et al Arch Intern Med. 2005;165:1600-1605.





NALTREXONE

- For opiate abusers
 - Marketed as **Trexan®** in the past
 - Opiate receptor blocker or antagonist
 - Long lasting effect after oral dosing (1- 3 days)



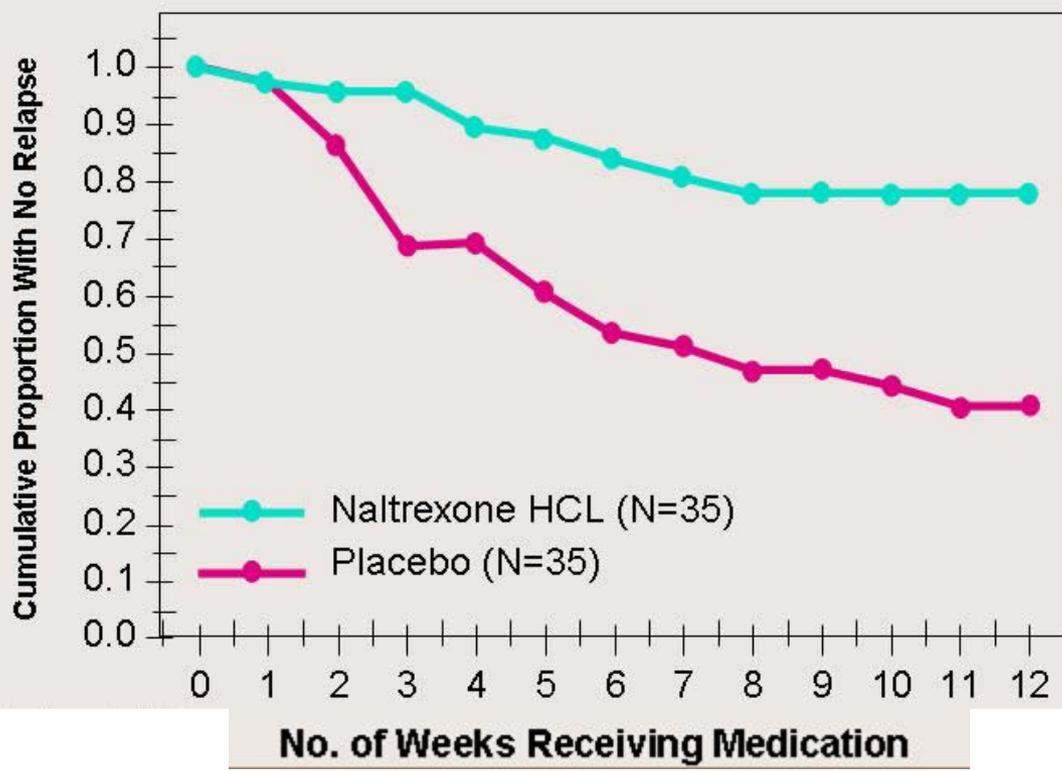
NALTREXONE

- For alcohol abusers
 - Marketed as **Revia®** since 1994
 - New formulation, approved in 2006, is **Vivitrol®**, which is given by injection and the effect lasts 4 weeks
 - Blocks pleasurable effects of alcohol (attenuates stimulatory effects) and reduces craving
 - In one study, medication for 10 weeks; **abstinence increased from 37% in control group to 89%.**
 - If subjects did drink, the number of drinks dropped from 9.5 to 2.5



NALTREXONE IN THE TREATMENT OF ALCOHOL DEPENDENCE

Cumulative Relapse Rate - Showing improvement over placebo

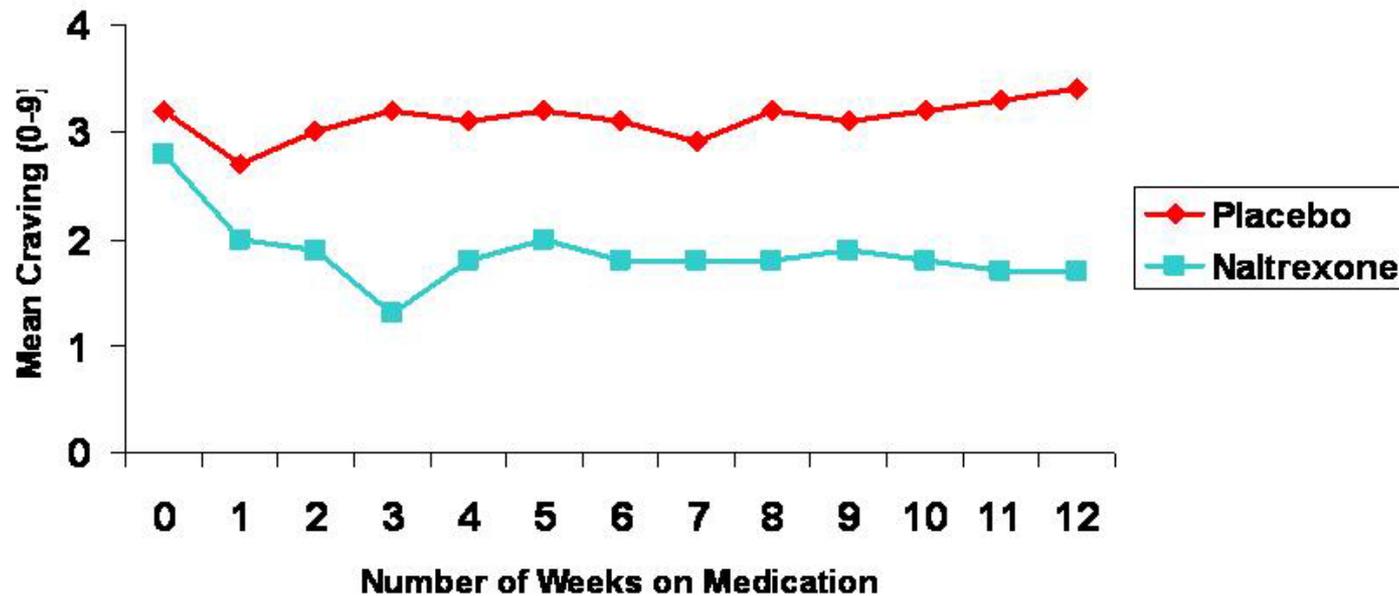


Volpicelli et al., 1992



MEAN CRAVING SCORES

(shows less craving with naltrexone)

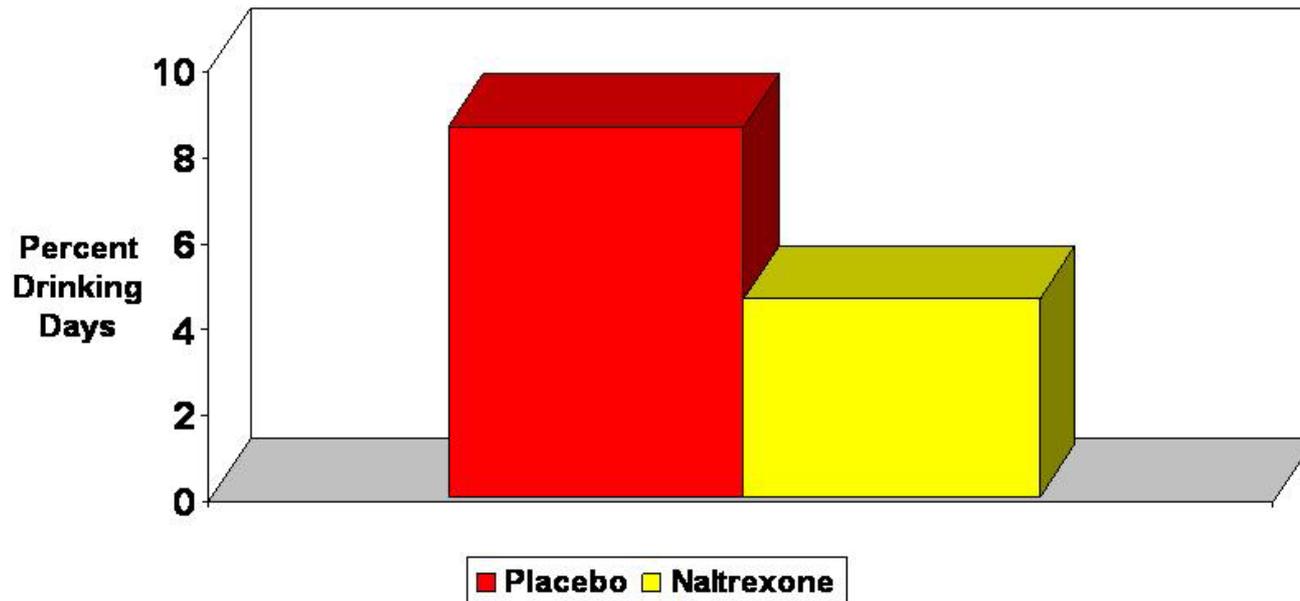


Volpicelli et al., 1992



DRINKING DAYS WHILE ON MEDICATION

(shows less drinking days while on naltrexone)



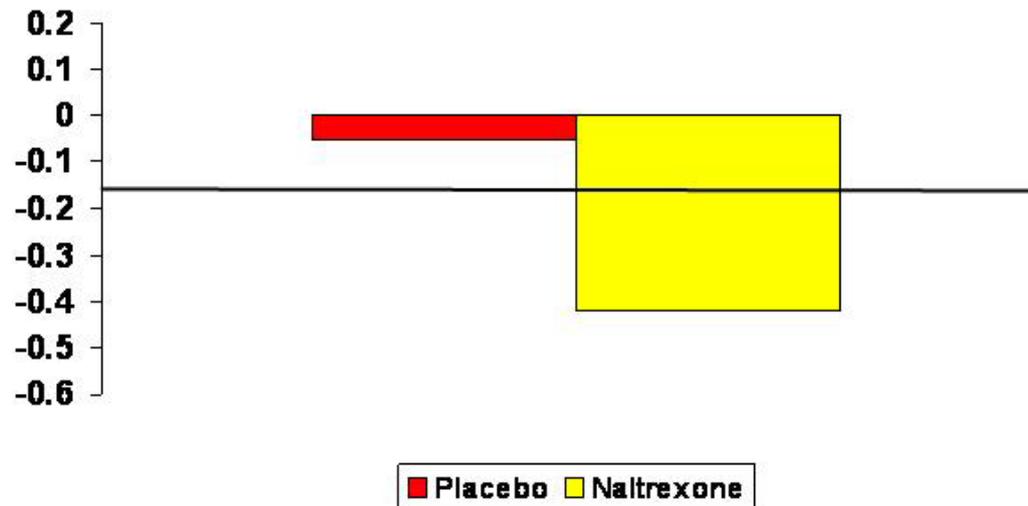
Volpicelli 1992, 1994



SUBJECTIVE "HIGH"

(blocked opiate receptor effect)

+1 = increased high
0 = no change in high
-1 = decreased high



Volpicelli 1992, 1994



NALTREXONE

- Safe
- Most common side - effect is nausea
- Liver can be affected at high doses
- Counseling and support groups should accompany the use of this medication



SIDE EFFECTS WITH 50 MG/DAY NALTREXONE

| | Months 1-3 | |
|----------------------------|--------------------|-----------------|
| | Naltrexone N=54 | Placebo N=45 |
| Headaches | 20.4 | 11.1 |
| Agitation/Anxiety | 16.7 | 17.8 |
| Nausea | 13.0 | 4.4 |
| Vomiting | 0 | 2.2 |
| Increased Sexual Desire | 14.8 | 15.6 |

Volpicelli et al., 1995



SIDE EFFECTS WITH 100 MG/DAY NALTREXONE

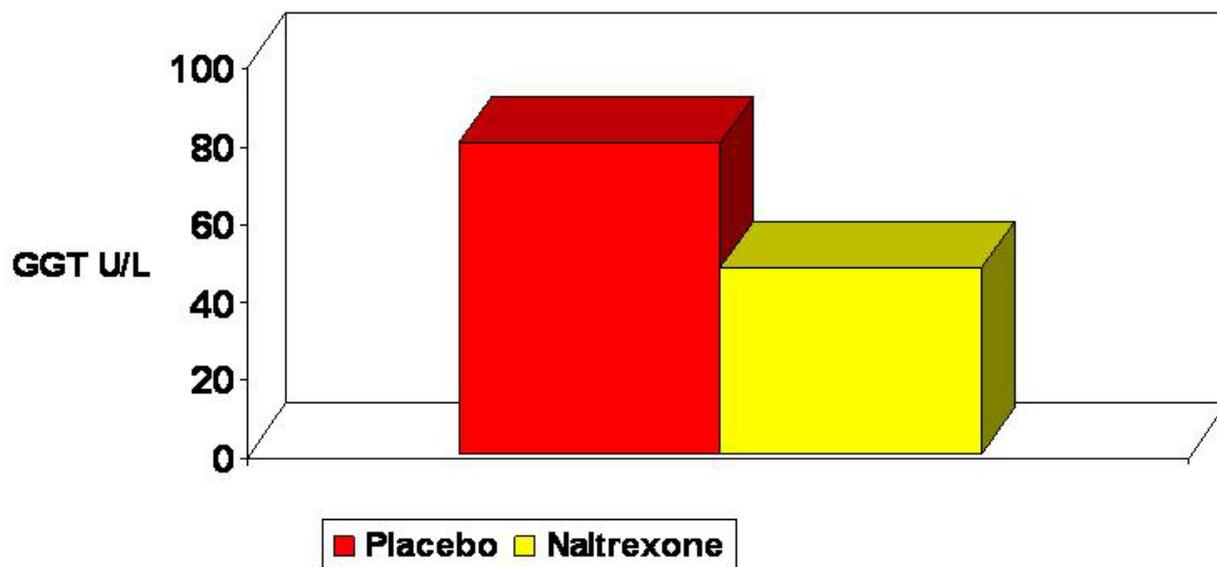
| | Months 1-3 | |
|----------------------------|---------------------|-----------------|
| | Naltrexone N=119 | Placebo N=61 |
| Headaches | 19.3 | 13.1 |
| Agitation/Anxiety | 10.1 | 13.1 |
| Nausea | 11.8 * | 3.3 |
| Vomiting | 6.7 | 1.6 |
| Increased Sexual Desire | 5.9 | 6.5 |

Volpicelli et al., 2001



GGT VALUES AT THE END OF THE STUDY

(show that the liver actually improves,
probably due to decrease in alcohol use)



Volpicelli 1992, 1994



STARTING AND ENDING NALTREXONE TREATMENT

- There may be fewer side effects with naltrexone when initiated following alcohol detoxification
- Short-term naltrexone treatment (3 months) may not be as effective as long-term treatment
- The use of cognitive behavioral therapy in conjunction with naltrexone treatment may provide synergistic effects when naltrexone is stopped
- Naltrexone may be used on an as-needed basis following a course of daily naltrexone



NALTREXONE

- Clinical trials of effectiveness (randomized and placebo controlled)
 - Initial was Volpicelli and O'Malley
 - 6 studies found naltrexone effective though relapse definition differed (5 or > drinks on 1 occasion, 5 or > drinking occasions in 1 week, arriving at clinic intoxicated)
 - 1 found naltrexone not effective
 - Meta - analysis: moderately effective
 - Krystal et al in the New England Journal of Medicine - Dec 13, 2001
 - Not effective in men with chronic, severe alcohol dependence



NALTREXONE

- Clinical trials ongoing in special populations
 - Combination with SSRI's (selective serotonin reuptake inhibitors such as Prozac), acamprosate, and ondansetron
 - Early problem drinkers
 - Alaskan natives
 - Eating disorder patients
 - PTSD patients
 - Nicotine dependent patients



CONCLUSIONS

- Especially effective in subjects with a strong family history of alcoholism, high levels of initial craving, and for subjects who reliably take the medication
- Safe in doses up to 100 mg per day



CONCLUSIONS

- Effective in a variety of treatment settings including primary settings where motivation to stay in treatment and take medications is supported
- Long-term treatment (9 months) is more effective than short-term treatment (3 months)



VIVITROL

- Manufacturing and Marketing is being carried out in a combined effort by Alkermes and Cephalon.
- Vivitrol, naltrexone for extended – release is a formulation that uses microspheres that can be administered by intramuscular injection.
- The dose of 380 mg is designed to be injected once every 4 weeks.



NON FDA APPROVED USES

- Transdermal naltrexone delivery is desirable in the treatment of narcotic dependence and alcoholism.
 - The purpose of this study was to increase the delivery rate of naltrexone (NTX) across human skin by using a novel prodrug.
 - A duplex "gemini" prodrug (precursor to the drug) of naltrexone was synthesized and evaluated.
 - The prodrug was hydrolyzed on passing through the skin and appeared mainly as naltrexone in the receiver compartment.
 - Due to the design of this prodrug, toxicities associated with this compound should be nonexistent, because only naltrexone and carbon dioxide (carbonic acid) are released when the prodrug is cleaved into its two parts.

(Hammell DC; Hamad M; Vaddi HK; Crooks PA; Stinchcomb AL . J Control Release. 2004; 97(2):283-90)



NON FDA APPROVED USES

- Naltrexone effective for smoking cessation in women
 - Randomized, double-blind placebo controlled trial using patches and psychosocial therapy in all; 50 mg naltrexone per day and followed for 12 weeks
 - 44 women total
 - 55% of subjects completed
 - 92% of naltrexone treated subjects were successful vs 50% in the placebo group
 - There was no effect on retention rates



NON FDA APPROVED USES

- Low dose naltrexone
 - Research ongoing to evaluate the effect on the treatment of HIV and cancer
 - Boosts the immune system
 - Increased endorphin and enkephalin levels
 - 3 - 4.5 mg dose every evening



NALTREXONE OR SPECIALIZED ALCOHOL COUNSELING AN EFFECTIVE TREATMENT FOR ALCOHOL DEPENDENCE WHEN DELIVERED WITH MEDICAL MANAGEMENT

- The medication naltrexone and up to 20 sessions of alcohol counseling by a behavioral specialist are equally effective treatments for alcohol dependence when delivered with structured medical management, according to results from "Combining Medications and Behavioral Interventions for Alcoholism" (The COMBINE Study).
- Results from the National Institutes of Health-supported study show that patients who received naltrexone, specialized alcohol counseling, or both demonstrated the best drinking outcomes after 16 weeks of outpatient treatment.
- All patients also received Medical Management (MM), an intervention consisting of nine brief, structured outpatient sessions provided by a health care professional.



NALTREXONE OR SPECIALIZED ALCOHOL COUNSELING AN EFFECTIVE TREATMENT FOR ALCOHOL DEPENDENCE WHEN DELIVERED WITH MEDICAL MANAGEMENT

- Contrary to expectations, the researchers found no effect on drinking of the medication acamprosate and no additive benefit from adding acamprosate to naltrexone.
- During the 16 weeks of treatment and 1 year after the treatment, the researchers assessed the patients for the percentage of days abstinent from alcohol and time to the first heavy drinking day, defined as 4 or more drinks per day for women and 5 or more drinks per day for men. They also assessed the odds of good clinical outcome, defined as abstinence or moderate drinking without alcohol-related problems. As in other large clinical trials, the researchers found that most patients showed substantial improvement during treatment and that both the overall level of improvement and the differences between treatment groups diminished during the follow-up period. In the COMBINE study, however, naltrexone continued to show a small advantage for preventing relapse at 1 year after the end of active treatment.





NICOTINE REPLACEMENT THERAPIES (NRT)

- Nicotine gum (nicotine polacrilex, Nicorette®)
- Nicotine transdermal patches (Habitrol®, Nicoderm CQ® , Nicotrol®)
- Nicotine inhaler (Nicotrol inhaler®)
- Nicotine spray (Nicotrol ns®)
- Nicotine lozenge (Commit®)



NICOTINE REPLACEMENT THERAPIES (NRT)

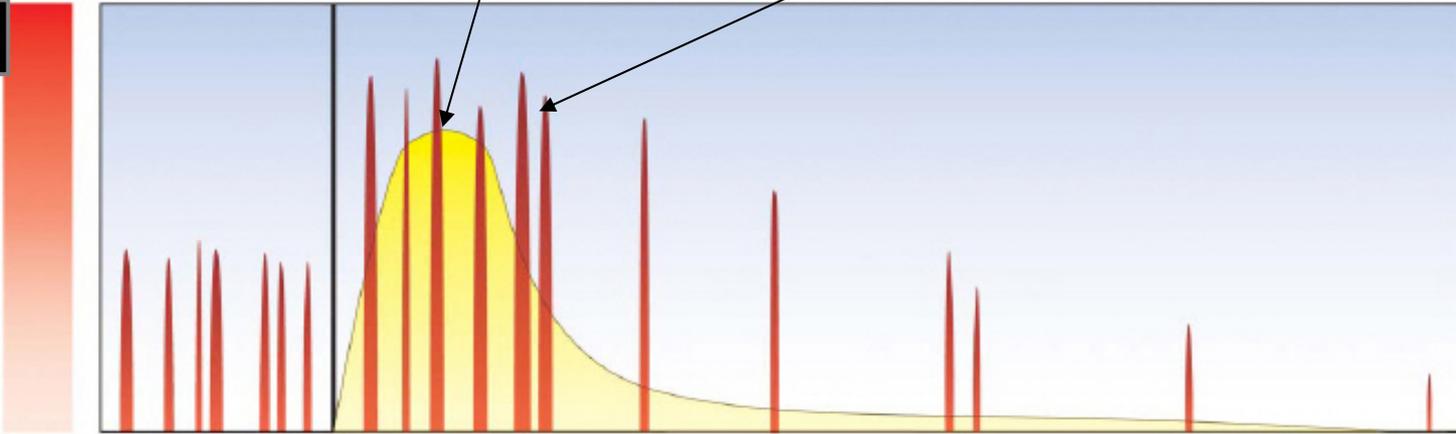
- Developed in Sweden during the 1970's as a means to assist submariners
- Cornerstone of tobacco dependence treatment
 - Safe
 - Effective



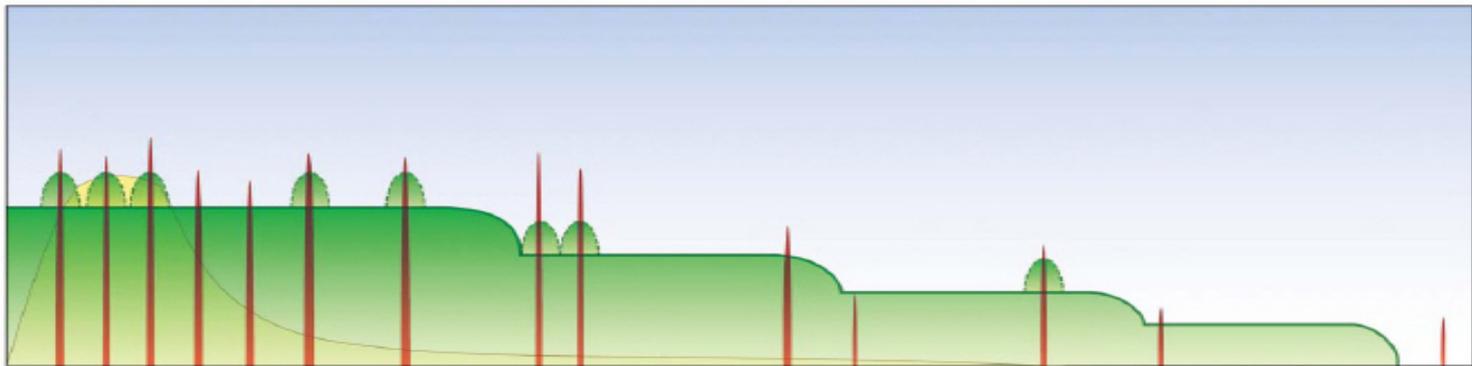
MEDICATION: EFFECTS ON WITHDRAWAL & URGES

Stop Date

Intensity



Intensity



LESS INTENSE WITHDRAWAL AND URGES WITH RX

TIME



NICOTINE REPLACEMENT THERAPIES (NRT)

- Nicotine gum (nicotine polacrilex, Nicorette®)
 - Approved by the FDA in 1984
 - Available in 2mg (less than 25 cigarettes per day) and 4mg pieces (more than 25 cigarettes smoked in a day)
 - .86 mg absorbed from the 2mg piece
 - 1.2 mg absorbed from the 4 mg piece
 - Composed of nicotine bound to an ion-exchange resin and then incorporated into a gum base
 - “Park and chew” technique
 - Do not chew like regular gum
 - Releases peppery taste, then “park” it on the side of the mouth
 - Each piece should last 30 minutes



NICOTINE REPLACEMENT THERAPIES (NRT)

- Nicotine gum (nicotine polacrilex, Nicorette®)
 - Affected by chewing rate and pH of the saliva
 - Do not eat or drink food around the time of gum use
 - Adverse effects: jaw pain, mouth soreness, dyspepsia, hiccups
 - Patient uses 1 – 2 pieces per hour for the first 6 weeks then tapers down use slowly
 - 24 pieces per day is maximum use



NICOTINE REPLACEMENT THERAPIES (NRT)

- NICOTINE TRANSDERMAL PATCHES (HABITOL® , NICODERM CQ ®, NICOTROL ®)
 - Approved by the FDA in 1991
 - Over the counter approval in 1996
 - All 21 mg patches deliver .9mg of nicotine per hour
 - Temperature and circulation affect delivery
 - Adverse effects: sleep disturbance, skin reactions (rash)



NICOTINE REPLACEMENT THERAPIES (NRT)

- NICOTINE TRANSDERMAL PATCHES (HABITOL® , NICODERM CQ ® , NICOTROL ®)
 - Individualize treatment
 - Less than 10 cigarettes per day consider a 7 mg patch
 - 10 to 15 cigarettes per day consider a 14 or 21 mg patch
 - 15 to 20 cigarettes per day consider a 21 mg patch
 - If high use, consider multiple patches
 - Always consider at least 2 different pharmacotherapies for better results



THE PATCH AND SMOKING



- Nicoderm and Habitrol study
 - 1800 patients
 - 60% smoked with the patch on

NO CORONARY EVENTS



USE OF NRT AND THE RISK OF ACUTE MI, STROKE AND DEATH

- STUDY BY HUBBARD ET AL IN TOBACCO CONTROL 2005
 - 33247 individuals given NRT's
 - 861 had a heart attack
 - 506 had a stroke
 - There was a progressive increase in the incidence of first heart attack in the 56 days leading up to the first NRT use, but the incidence fell after this time and was not increased in the 56 days after starting the NRT.
 - Results similar in patients with stroke and a second heart attack and for subgroups of patients with hypertension and angina



NICOTINE PATCH THERAPY INITIAL DOSING GUIDELINES

Based on Baseline Cigarettes/Day

| | |
|-----------|------------|
| <10 CPD | 7-14 mg/d |
| 10-20 CPD | 14-21 mg/d |
| 21-40 CPD | 22-42 mg/d |
| >40 CPD | 42+ mg/d |



INITIAL DOSING GUIDELINES: SMOKELESS TOBACCO

| Cans/Pouches/Week | Mg NRT/day |
|-------------------|------------|
| > 3 | 42+ |
| 2-3 | 33-44 |
| 1-2 | 21-33 |
| < 1 | 11-22 |



NICOTINE PATCH AND ALCOHOL

- Duke University research
 - Found small amounts of alcohol can enhance the pleasurable effects of nicotine
 - Add mecamylamine to patch
 - Antihypertensive, nicotine antagonist, if used with nicotine patch – 37.5% 12 month abstinence rates (Rose et al 1994)
 - Can impact on alcohol consumption and smoking



NICOTINE REPLACEMENT THERAPIES (NRT)

- NICOTINE INHALER (NICOTROL INHALER ®)
 - FDA approved in 1998
 - Cigarette holder shape with replaceable cartridges (puff not inhaled)
 - Each contains 10 mg nicotine and 1 mg menthol
 - 400 puffs per cartridge delivering 13 ug per puff
 - 80 puffs equal one cigarette
 - Use 4 - 6 inhalers per day
 - AFFECTED BY PUFF RATE, TEMPERATURE, SALIVA pH
 - 25% taper every month in number of puffs



NICOTINE REPLACEMENT THERAPIES (NRT)

- NICOTINE SPRAY (NICOTROL NS ®)
 - Approved by the FDA in 1996
 - One inhalation in each nostril = total dose of 1mg
 - Average use is 13 - 20 doses per day
 - Adverse effects: running nose, nasal irritation, throat irritation, watery eyes, sneezing
 - All but throat irritation decrease in 1 - 7 days



NICOTINE REPLACEMENT THERAPIES (NRT)

- NICOTINE LOZENGE (COMMIT ®)
 - Approved by the FDA in 2002, though described as early as the 1960's
 - 2mg and 4 mg doses (72 lozenge package)
 - Maximum number is 20 lozenges per day
 - Glaxo packages “time to first cigarette” program with lozenges - program to decide if patient should start with a 2 or 4 mg lozenge



NICOTINE LOZENGE

- Efficacy: Doubles to triples 12 month cessation
- Dosage
 - 2 mg-for those smoking >30 min after waking
 - 4 mg-for those smoking <30 min after waking
- First 6 weeks 1 lozenge every 1-2 hrs
- Weeks 7-10 1 lozenge every 2-4 hrs
- Weeks 11-12 1 lozenge every 4-8 hrs



EFFICACY OF NICOTINE GUM (N = 13 STUDIES)

| Pharmacotherapy | Odds Ratio 95% (CI) | Estimated Abstinence Rate |
|------------------------------|------------------------|------------------------------|
| Placebo (reference group) | 1.0 | 17.1% |
| Nicotine Gum | 1.5 (1.3 – 1.8) | 23.7% |



EFFICACY OF NICOTINE INHALER (N = 4 STUDIES)

| Pharmacotherapy | Odds Ratio 95% (CI) | Estimated Abstinence Rate |
|------------------------------|------------------------|------------------------------|
| Placebo (reference group) | 1.0 | 10.5% |
| Nicotine Inhaler | 2.5 (1.7 – 3.6) | 22.8% |



EFFICACY OF NICOTINE NASAL SPRAY (N = 3 STUDIES)

| Pharmacotherapy | Odds Ratio 95% (CI) | Estimated Abstinence Rate |
|------------------------------|------------------------|------------------------------|
| Placebo (reference group) | 1.0 | 13.9% |
| Nicotine Nasal Spray | 2.7 (1.8 – 4.1) | 30.5% |



EFFICACY OF NICOTINE PATCH (N = 27 STUDIES)

| Pharmacotherapy | Odds Ratio 95% (CI) | Estimated Abstinence Rate |
|------------------------------|------------------------|------------------------------|
| Placebo (reference group) | 1.0 | 10.0% |
| Nicotine Patch | 1.9 (1.7 – 2.2) | 17.7% |



EFFICACY OF COMBINATION NRT (N = 3 STUDIES)

| Pharmacotherapy | Odds Ratio 95% (CI) | Estimated Abstinence Rate |
|------------------------------|------------------------|------------------------------|
| One NRT (reference group) | 1.0 | 17.4% |
| Two NRTs | 1.9 (1.3 – 2.6) | 28.6% |



IS HIGHER DOSE PATCH THERAPY SAFE?

- Hughes et al, 1999, N&TR
 - 1039 smokers
 - 0, 21, 35, and 42 mg/d
 - 6 weeks/10 week taper
 - No difference in adverse events
- Fredrickson et al., 1995, Psychopharm
 - 40 smokers
 - > 20 cpd
 - 22 mg/d & 44 mg/d for 4 weeks
 - Safe, tolerable, no adverse effects



IS HIGHER DOSE PATCH THERAPY SAFE?

- Jorenby et al., 1995, JAMA
 - 504 smokers
 - 22 mg/d or 44 mg/d for 8 weeks (4/4)
 - Adverse effects
 - Nausea (28% vs. 10%, $P < .001$)
 - Vomiting (10% vs. 2%, $P < .001$)
 - Erythema (redness)(30% vs. 13%, $P < .01$)



FINDINGS FROM DOSE RANGING STUDY

| Dose associated with cessation @ 8 weeks | | | |
|---|----------------|-----------------|---------------|
| | 8 weeks | 6 months | 1 year |
| 11mg | 59% | 59% | 41% |
| 22mg | 62% | 54% | 35% |
| 44mg | 100% | 78% | 67% |

Dale, et al. *JAMA*, 1995.



PERCENTAGE “REPLACEMENT” MAYO CLINIC MODEL

Model used the amount of cotinine in the smokers blood (metabolyte of nicotine) to determine amount of patch dose needed to recreate the cotinine level.

$$\frac{\text{venous cotinine on NRT}}{\text{venous cotinine while smoking}} \times 100$$

Goal = 100%

*COTININE LEVELS CAN BE DRAWN AT ANY TIME THROUGHOUT THE DAY



HIGHER DOSE NICOTINE PATCH

- There is a dose-response effect
- Long-term abstinence improved
- Treatment-related adverse events are uncommon
- Withdrawal symptoms less with higher dose NRT

***Cochrane Database of Systematic Reviews 2005**



CARDIOVASCULAR TOXICITY

- Mechanisms of cardiac toxicity smoking cigarettes
 - Induction of a hypercoagulable (increased blood clots) state.
 - Increased myocardial work.
 - Carbon monoxide-mediated reduced oxygen carrying capacity of the blood.
 - Catecholamine (epinephrine and norepinephrine) release.



CARDIOVASCULAR TOXICITY

- Dose of nicotine from NRT and cardiovascular response is flat.
- Implication: The effects of cigarette smoking in conjunction with NRT are similar to those of cigarette smoking alone

(Benowitz NL, Gourlay SG J Am Coll Cardiol 1997;29:1422-31)



WHAT IF THEY ARE ON NRT & SMOKE?

- Concern about this is not supported by data.
- Joseph took a high risk cardiac group and put them on patch or placebo.
 - 49% with active angina
 - 40% with history of heart attack
 - 35% with history of cardiac bypass
 - No increase in cardiac events for the patient group
 - 21% of the patients were not smoking at the end vs 9% of the placebo group.

(Joseph AM. NEJM 335:1792-8, 1996 & Jiminez-Ruiz. Respiration 69:452-6, 2002)



WHAT IF THEY ARE ON NRT & SMOKE?

- Concern about this is not supported by data.
- Jiminez-Ruiz put severe COPD patients on nicotine gum
 - Most patients continued to smoke, though less.
 - No adverse events attributed to nicotine.
 - COPD (chronic obstructive pulmonary disease) got better



NRT WITH CARDIOVASCULAR DIAGNOSIS

- 5 week placebo controlled trial: 14-21mg/day.
- 156 pts with cardiac disease
- Cardiac symptoms monitored, 24h ECG
- Concomitant smoking with patch
- ECG monitoring: No differences in arrhythmias or ST segment depression

(Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease Arch Int Med 154 (1994), pp. 989-995)



CARDIOVASCULAR EFFECTS

- Nicotine may stimulate sympathetic neural pathways and cause systemic catecholamine release.
- Cardiovascular effects from smoking greater than with NRT.
- NRT plus smoking equivalent to smoking

(Benowitz NL, Gourlay SG J Am Coll Cardiol 1997;29:1422-31)



CARDIOVASCULAR EFFECTS

- “Thus, caveats within the 1994 European Guidelines for Preventive Cardiology regarding the need for caution when using nicotine replacement therapy in patients with cardiovascular disease requires revision”

(Balfour D, Benowitz N, Fagerstrom K, Kunze M, Keil U. European Heart Journal (2000) 21, 438-445)



CARDIOVASCULAR EFFECTS – OTHER REFERENCES

- Murray RP, Bailey WC, Daniels K. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. *Chest* 1996; 109:438-45
- Mahmarian JJ, Moye LA, Nasser GA. Nicotine patch therapy in smoking cessation reduces the extent of exercise –induced myocardial ischemia. *J Am Coll Cardiol* 1997; 30:125-30
- Benowitz NL, Gourlay SG Cardiovascular toxicity of nicotine: Implications for nicotine replacement therapy. *J Am Coll Cardiol* 1997; 29:1422-31





ZYBAN®

- Generic form= bupropion hydrochloride
- Marketed first as an antidepressant
 - Wellbutrin® & Wellbutrin SR ®
- **First non-nicotine medication approved for smoking cessation**



ZYBAN®

- Appears to work through the dopamine and norepinephrine pathways to reduce craving
- Can be used alone or in combination with nicotine replacement medications
- Side effects
 - Dry mouth
 - Insomnia
 - NEJM 2002 – seizure induced by insufflation of bupropion – case report of adolescent who crushed six 150mg tablets and snorted them



ZYBAN®

- Had significant success in whites, work by JS Ahluwalia in JAMA 2002;288:468-474 showed that this medication can be effective in African - American patients
 - Reservations to this finding are due to differences in white and African - American smokers
 - African - American smokers tend to:
 - Smoke fewer cigarettes per day
 - Be more likely to smoke mentholated cigarettes
 - Smoke brands with higher tar and nicotine contents and thus are more highly addicted to nicotine
 - Be slower nicotine metabolizers



ZYBAN®

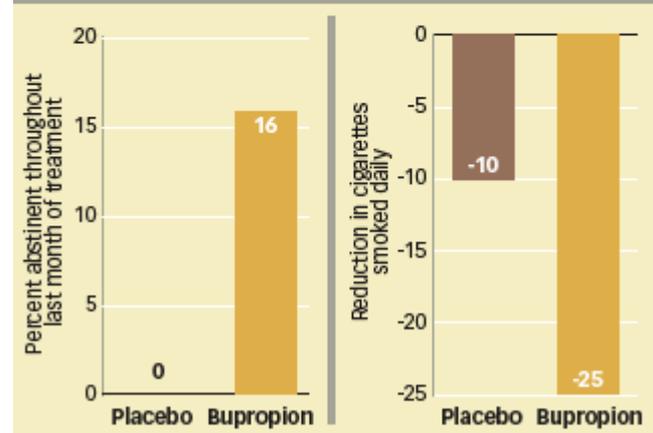
- May be useful in people who have a tendency to gain weight
 - Univ. of Penn Lerman et al 2004
 - There is a variant of the dopamine D2 receptor gene whereby some people show an increase value of food reward after stopping smoking and gain weight



ZYBAN®

- May be useful for people with schizophrenia
 - NIDA funded study at Massachusetts General Hospital found that those people with schizophrenia who were given Zyban, were more likely to achieve continuous abstinence for a month than those receiving placebo
 - 53 patients
 - All received weekly group cognitive – behavioral therapy and 300 mg of Zyban or placebo

BUPROPION ENHANCES OUTCOME OF COGNITIVE-BEHAVIORAL THERAPY Patients with schizophrenia who participated in weekly group cognitive-behavioral therapy for smoking cessation were more likely to remain abstinent throughout the last month of a 12-week study if they also took bupropion. Among patients still smoking at study's end, those receiving bupropion smoked fewer cigarettes daily than those on placebo.



ZYBAN®

- Contraindicated in patients
 - Bulimia (high incidence of seizures if Zyban used with this eating disorder)
 - Seizure disorders



COMBINATION NRT

Combine long-acting patch with “as needed” short-acting medication (gum, lozenge, inhaler, nasal spray)

- Encourages patient to be in control of cravings and withdrawal symptoms
- Improves compliance with treatment plan
- Achieves higher drug concentrations
- Allows further dose adjustments
- Provides an alternative to tobacco

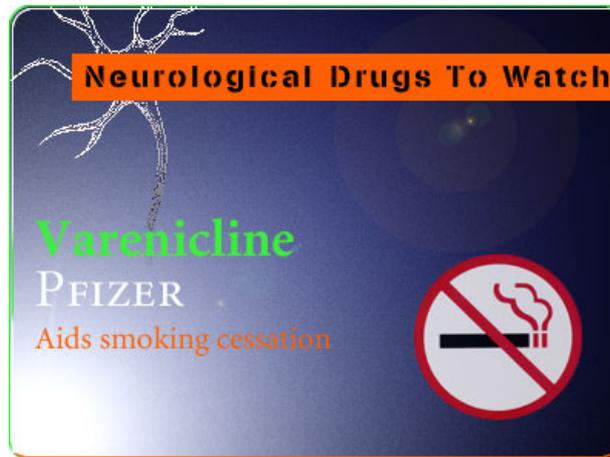


NRT AND TEENS (VERY FEW ADOLESCENT STUDIES)

- Stanford Univ. School of Med study 2004
 - 211 teens (15-18), minimum 10 cigarettes/d
 - Nicotine patch and Zyban
 - Nicotine patch and placebo
 - All received behavioral skills training
 - At 10 weeks 23% of combined group quit completely and 28% of patch/placebo group quit
 - At 26 weeks only 8% and 7% respectively were still abstinent
 - Harder for teens to quit?



VARENICLINE



- Varenicline is a drug which stimulates nicotine receptors in the brain without itself being addictive.
- Developed by Pfizer Pharmaceuticals and marketed as Chantix after FDA approval in 5/06, varenicline is a nicotine partial receptor agonist (partial effect when bound to the receptor) which comes in pill form to prevent withdrawal symptoms in people attempting to quit smoking and decreasing the pleasure associated with smoking.



7-WEEK TRIAL: SAFETY AND TOLERABILITY OF VARENICLINE

- Nausea was the most common adverse experience (AE) related to varenicline and was mainly mild to moderate in severity.
- Percent discontinued due to any treatment emergent AE.
 - 0.3 mg varenicline once daily = 14.3%
 - 1.0 mg varenicline once daily = 12.7%
 - 1.0 mg varenicline twice daily = 11.2%
 - 150.0 mg bupropion twice daily = 15.9%
 - Placebo = 9.8%
- It will be marketed as a twice a day medicine

(Oncken C, et al. (2005). Presented at the 2005 Meeting of the Society for Research on Nicotine and Tobacco. Prague, Czech Republic.)



RESULTS OF 12-WEEK PHASE 2 VARENICLINE DOSING TRIAL (N = 627)

- Weeks 9-12 continuous abstinence rates pooled by dose.
 - 1.0 mg twice daily doses = 50.6%
 - 0.5 mg twice daily doses = 45.1%
 - Placebo = 12.4%
- (Oncken C, et al. (2005). Presented at the 2005 Meeting of the Society for Research on Nicotine and Tobacco. Prague, Czech Republic.)



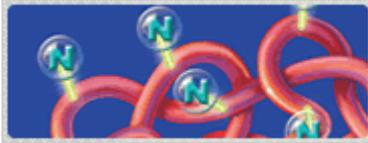
RESULTS OF EUROPEAN TRIALS

- Several studies conducted in Europe on about 2,000 smokers and presented in November at an American Heart Association conference showed that a year after initial treatment with varenicline, abstinence rates were 22 percent, versus 16 percent among those given Zyban and 8% on placebos.



NOVEL APPROACHES FOR THE FUTURE





Learn About **NicVAX**

A FUTURE APPROACH

- Nabi Biopharmaceuticals is developing NicVAX™ (Nicotine Conjugate Vaccine) a novel and proprietary investigational vaccine to prevent and treat nicotine addiction and as an aid to smoking cessation.
- In August 2003, Nabi Biopharmaceuticals initiated a Phase II clinical trial of NicVAX in the U.S. This double-blind, randomized, placebo-controlled study in 63 smokers
 - NicVAX is designed to cause the immune system to produce antibodies that bind to nicotine and prevent it from entering the brain.
 - These nicotine antibodies will act like a "sponge" soaking up nicotine as it circulates in the blood stream and preventing it from reaching the brain.
 - The positive stimulus in the brain that is normally caused by nicotine would then no longer be present.



XENOVA TA - NIC VACCINE

- A total of 60 subjects who smoked between 10 and 75 cigarettes a day were recruited into the trial, divided into three cohorts.
 - In the placebo group, 1 out of 12 participants (8%) reported being abstinent at their last visit or at 12 months compared with 3 out of 16 (19%) and 6 out of 16 (38%) in the two groups receiving the higher doses of TA-NIC.
 - Additionally, the proportion of participants who successfully made a quit attempt was higher amongst those receiving TA-NIC (95%) than amongst those receiving the placebo (73%).



ORAL NICOTINE REPLACEMENT

- The Straw™
 - 8 mg
- Recovery Pharmaceuticals
- Phase 3



THE STRAW™ TARGETS

- Oral delivery
 - An individual sips any beverage through The Straw™ and swallows the nicotine beads
 - The entire dose of nicotine is delivered in the first sip
- Manual stimuli
- Increased compliance
- Behavioral component



THE STRAW™ STATUS

- Phase 1 & 2 completed (1/02)
 - “The trial established that The Straw™ generated plasma levels of nicotine comparable to or higher than those seen with marketed nicotine replacement therapy products”
- Preparing for a pivotal Phase 3 trial

