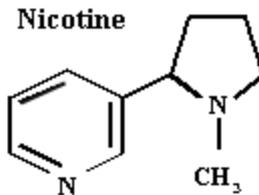


*“Science of Nicotine Replacement
Therapy and E-cigarettes”*
Tobacco Free Idaho Alliance
December 9th 2013

Roger Hefflinger, Pharm.D.
Clinical Associate Professor
ISU College of Pharmacy
Family Medicine Residency of Idaho



Characteristics Addictive Substance

WHO

- Primary Criteria:
 - Compulsive use
 - Psychoactive effects
 - Drug reinforced behaviors
- Additional Criteria:
 - Cravings
 - Use despite harm
 - Frequent relapse

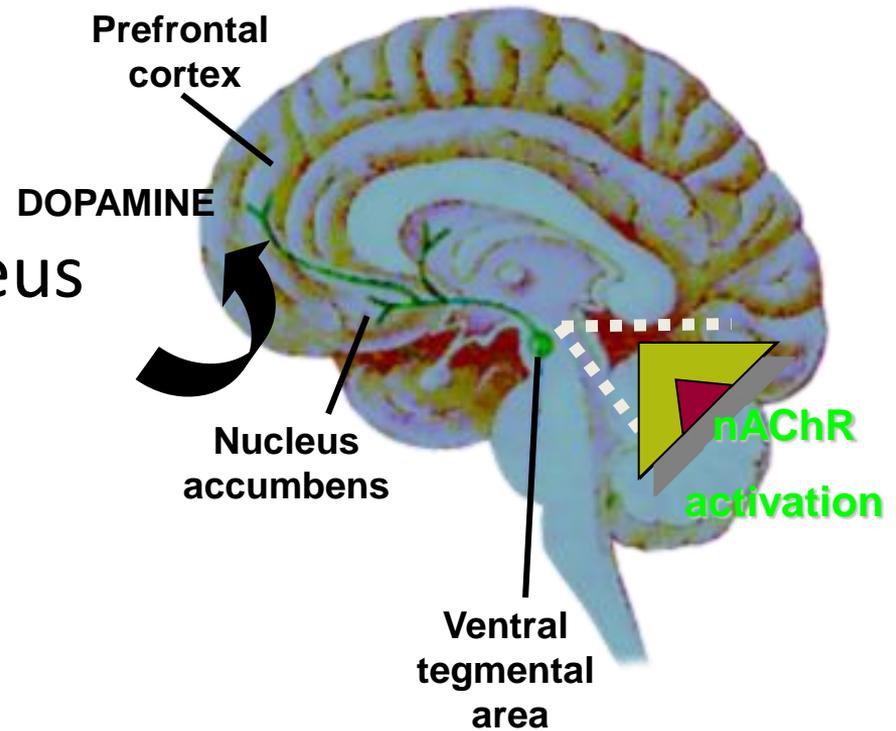


Pharmacology of Nicotine:

- Binds to Nicotinic acetylcholine receptors
- Rapidly crosses BBB
 - 8-10 seconds smoked
- Dose Dependent effects
- Rapid development of tolerance
- Low Dose:
 - central catecholamine release, increase in BP and increase in HR
 - Activation of nicotinic acetylcholine receptors = dopamine release
- High Dose:
 - peripheral effects, ganglionic stimulation
- Extremely High Dose:
 - Hypotension, slowing of HR

Smoking, Nicotine, and Neurochemistry

- Activates nicotinic acetylcholine receptors (nAChRs) in brain → dopamine release in nucleus accumbens
- Similar effects seen with other addictive drugs
- Critical component in addiction mechanisms



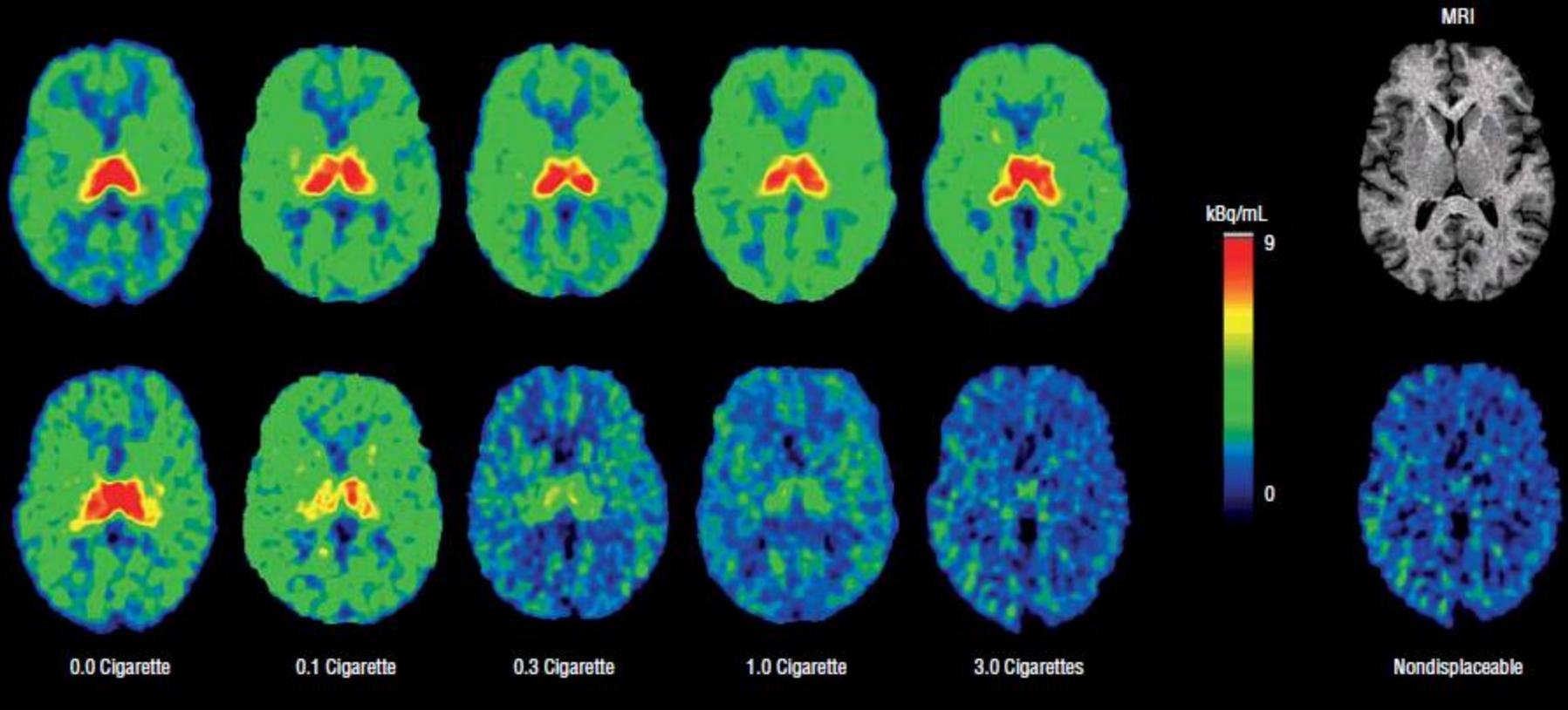


Figure 3. 2-[¹⁸F]fluoro-3-(2(*S*)-azetidylmethoxy) pyridine (2-F-A-85380) positron emission tomography (PET) images before (top row) and 3.1 hours after (bottom row) cigarette smoking. Images were obtained by averaging the six 10-minute frames over the 1 hour prior to the smoking break and by averaging the seven 10-minute scans from a mean of 3.1 hours after smoking the cigarette amount listed. The far right column shows a magnetic resonance image (MRI) of the brain and a PET image of nondisplaceable radioactivity distribution (calculated). All PET images were aligned to the level shown on the MRI.

Yellow and Green is Radiolabeled tracer binding to Alpha4Beta2 receptor:

Blue is displaced tracer at the amount nicotine delivered at 3 hours after dose:

Minimal smokers vs heavy smokers may have different biochemical responses

Controversy:

- Is it “Activation” or “Desensitization” of nicotinic acetylcholine receptors that contribute to behaviors related to nicotine addiction and mood?
- It is both
- Classic g-coupled proteins
- nAChRs- located throughout the brain
- Alpha subunits- 1-7
- Beta subunits- 1-9

Behavioral Effects of Nicotine:

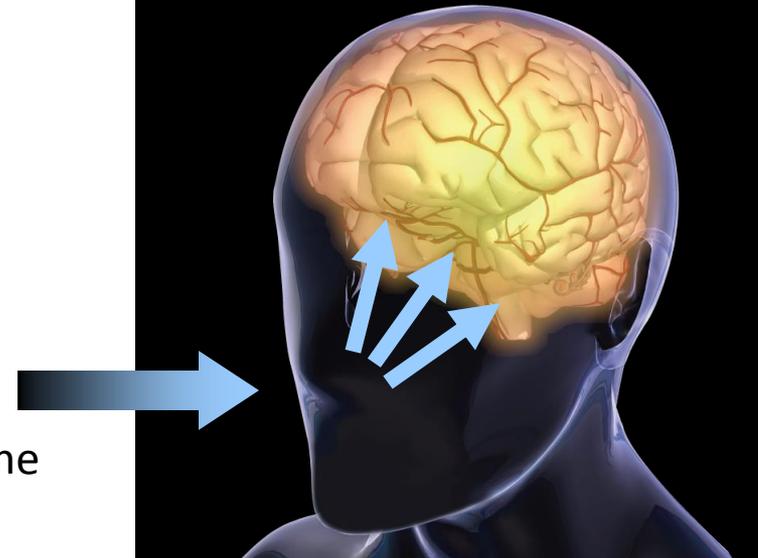
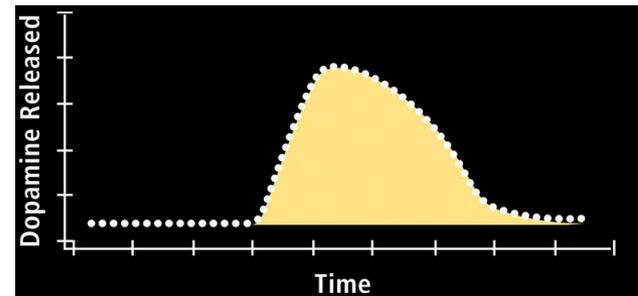
- Stimulatory action with first few “doses”
- Relaxation in stressful situations
- Improves mood
- Improves attention, learning and reaction times
- Self image and weight loss component



Why It's So Hard to Quit

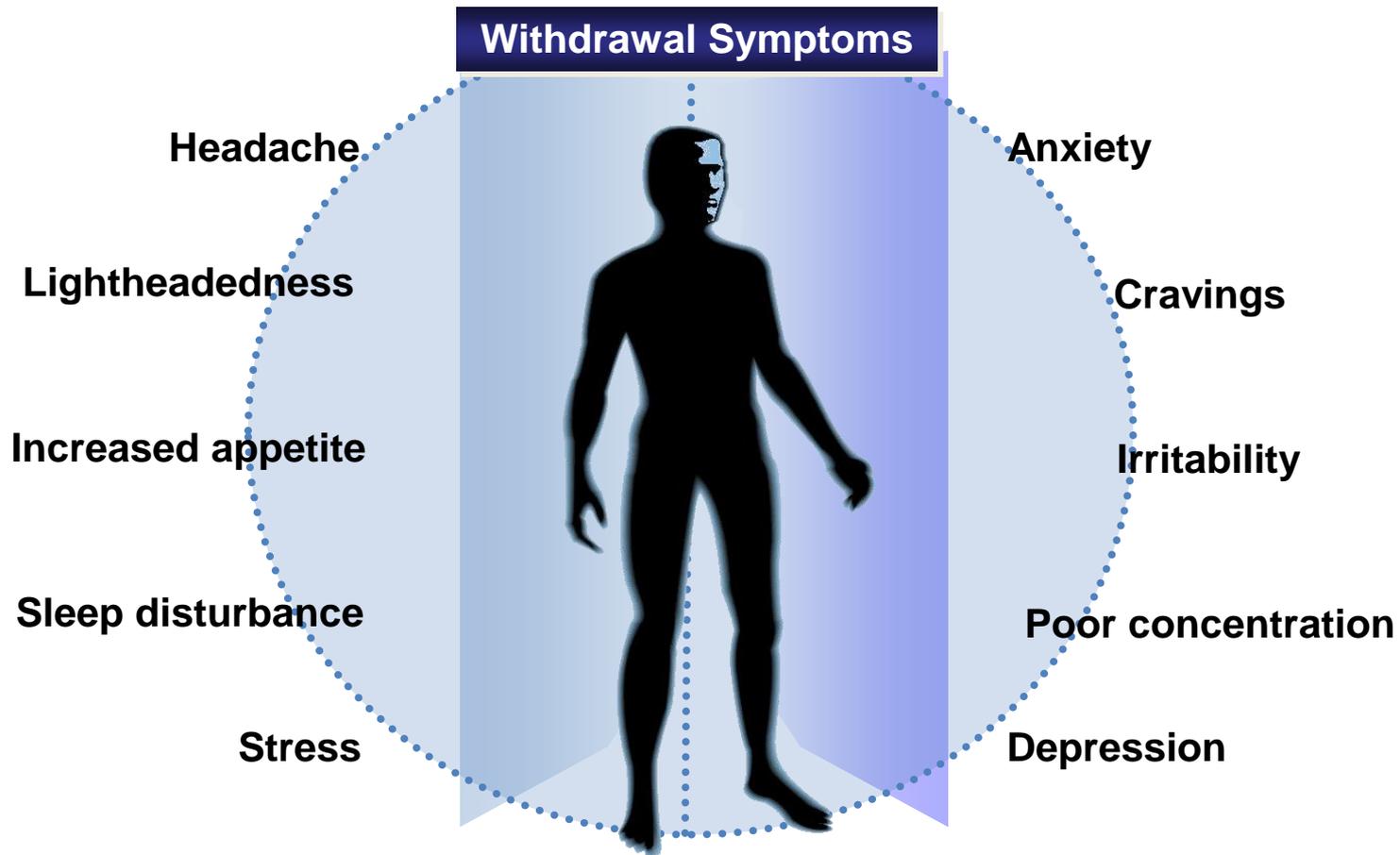
- **Smoking sends nicotine to the brain in a few seconds**
- **Nicotine starts a series of biochemical reactions that ultimately causes the release of dopamine, which gives a feeling of pleasure and calm**
- **Between cigarettes, the level of dopamine declines...and the smoker starts to experience withdrawal symptoms such as irritability and stress**
- **The brain craves nicotine to release more dopamine to bring it back to a level of pleasure and calm**
- **And the cycle continues as smoking again sends nicotine quickly to the brain**

Brain Dopamine



Nicotine

Nicotine Addiction From Cigarette Smoking Is Both a Physical and Psychological Condition, Making It Hard to Treat



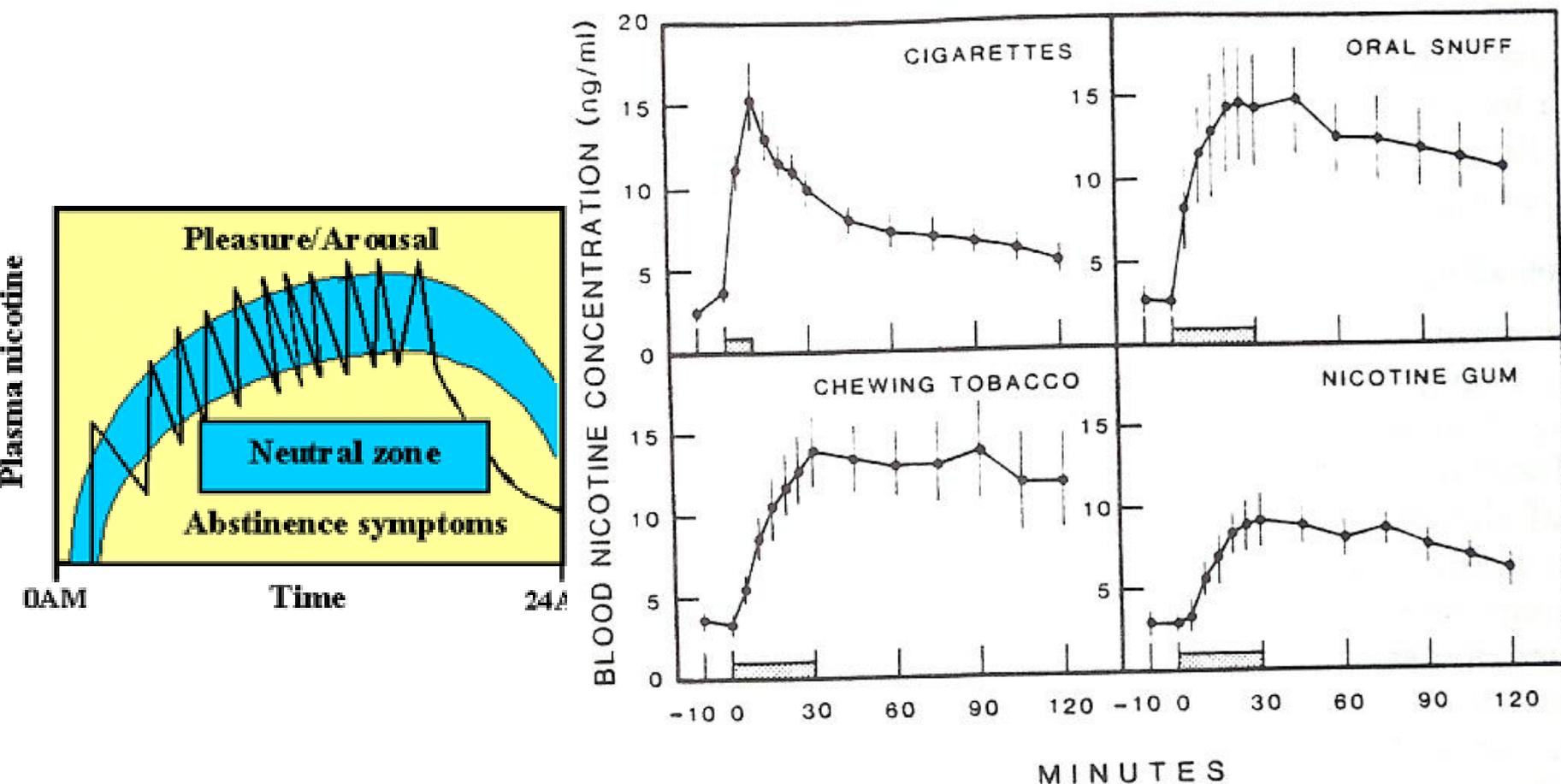


Figure 2. Mean (\pm SEM) Blood Concentrations of Nicotine in 10 Subjects Who Smoked Cigarettes for Nine Minutes ($1\frac{1}{3}$ Cigarettes), Used Oral Snuff (2.5 g), Used Chewing Tobacco (Mean, 7.9 g), and Chewed Nicotine Gum (Two 2-mg Pieces).

Shaded bars above the time axis indicate the period of exposure to tobacco or nicotine gum. (Reprinted from Benowitz et al.⁶³ with the permission of the publisher.)

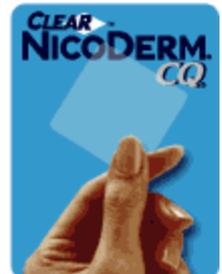
Low Tar and Nicotine:?

- 100% advertising
- Smokers will adjust the depth of inhalation and number of puffs (and cigs) to get and maintain serum levels
- 2006 Analysis:
 - Of 116 brands analyzed, 92 delivered more of the addictive substance in 2004 than in 1998. On average, 10 percent more nicotine is getting to smokers' lungs; three Doral 85 brands passed the 30 percent mark.
 - Cigarettes with the lowest levels: Doral Ultra-Light Kings and Winston Ultra-Light Kings.



Nicotine Replacement Therapy: NRT

- OTC-Transdermal
 - Nicoderm, Nicotrol
- OTC-Gum
 - Nicorette, Nicorette DS
- OTC- Lozenge
 - Commit
- RX-Inhaler
- RX-Nose Spray
- Electronic Cigarettes?



- **Myth #2:**

- Nicotine's addictive potential is the same regardless of whether nicotine is obtained through nicotine gum, the patch, or cigarettes.

- **Fact:**

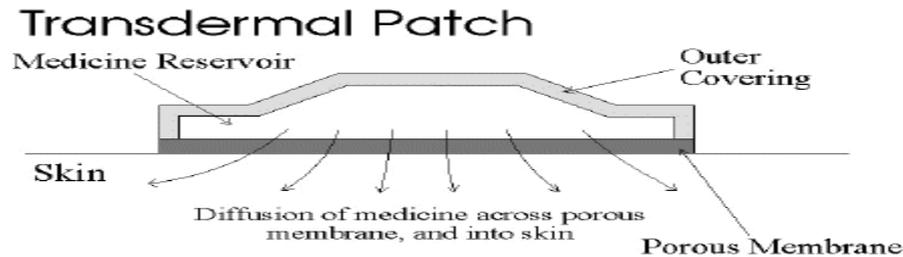
- Cigarettes are far more addictive than nicotine gum or the patch primarily because of the way in which they deliver nicotine.

- **Myth #5:**
 - Patients with heart disease should not use the nicotine patch or gum.
- **Fact:**
 - It is more dangerous for patients with heart disease to continue to smoke than to use NRT. Given the seriousness of their medical condition, cardiac patients who cannot quit should be among those first considered for NRT.

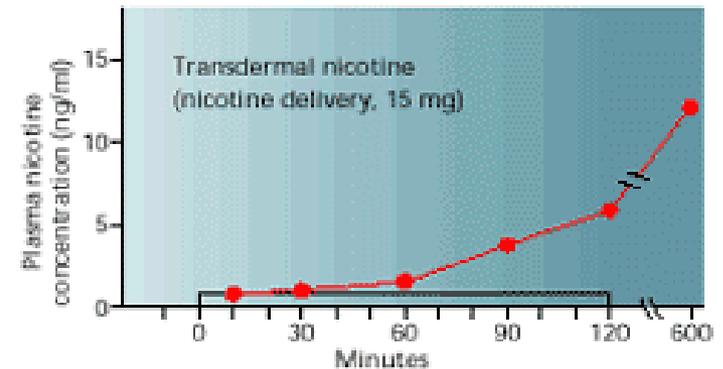
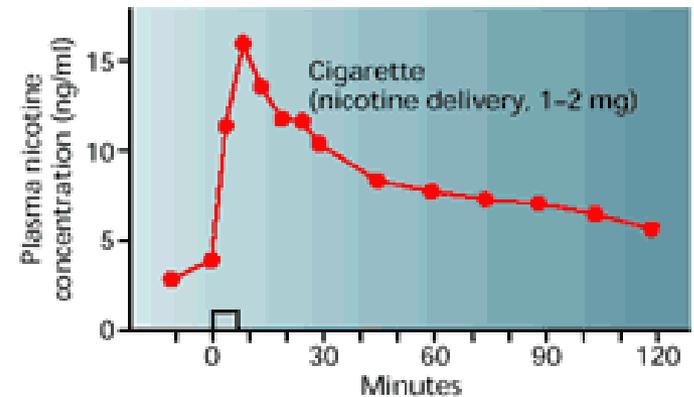
Transdermal Nicotine:



- Science: Actually Pharmaceuticals:



- Now OTC products:
- If > 20 cigarettes a day or users of smokeless tobacco:
 - Start at 21mg patch
 - Duration: 2-4 weeks
 - Then 14 mg patch
 - Duration 2-4 weeks
 - Then 7 mg Patch
 - Duration 2-4 weeks



Anticipated Efficacy:

- Nicoderm[®] (data from 1992 RX form)
 - 6 weeks of active treatment, 6 weeks of weaning off treatment and 12 weeks out follow-up
 - 9 centers (accounted for variation)
 - Once weekly follow-up support

<u>Nicoderm Delivery</u>	Number Patients	After 6 weeks	After Weaning	At 6 months
21	249	32-92%	18-63%	3-50%
14	254	30-61%	15-52%	0-48%
Placebo	253	15-46%	0-38%	0-35%

Anticipated Efficacy:

- Habitrol[®] (data from 1992 RX form)
 - 3 weeks titration?
 - 4 weeks of treatment
 - 3 weeks of taper
 - With or without concomitant support

Concomitant Support	Treatment	Number Patients	After 7 weeks	After Wean
Yes	<u>Habitrol</u>	260	19-54%	8-43%
Yes	Placebo	256	9-30%	8-30%
No	<u>Habitrol</u>	141	4-28%	4-20%
No	Placebo	135	0-24%	0-22%

- **Myth #12:**

- Use of the nicotine patch and gum should not exceed 3 months.

- **Fact:**

- The nicotine patch and gum should be used as long as needed to maintain or prolong tobacco abstinence.

Buccal: Nicorette Gum:

- 2 mg chews and 4 mg chews
- NOT A NORMAL GUM!!!!!!!!!!!!!!
- Few chomps- feel the tingle
 - Wait for nicotine absorption
 - Decrease the urge
- Remove the gum from mouth (or not)
 - depends on the addictions
- Repeat prn





Buccal: Commit[®]

<i>Step 1</i> <i>Weeks 1 to 6</i>	<i>Step 2</i> <i>Weeks 7 to 9</i>	<i>Step 3</i> <i>Weeks 10 to 12</i>
Initial treatment period	Step down treatment period	Step down treatment period
1 lozenge every 1-2 hours	1 lozenge every 2-4 hours	1 lozenge every 4-8 hours

- **What makes Commit[®] so different?**

First of all, Commit[®] is the first stop-smoking aid in the form of a lozenge. And Commit[®] uses a [groundbreaking dosage selector](#) based on how soon you smoke your first cigarette in the morning -- or Time to First Cigarette (TTFC) -- so you can make sure you choose the right strength when tailoring your own [personal quit program](#)

Available to help you quit
in stores and online.



“Ground Breaking Dosage Calculator”

2
mg

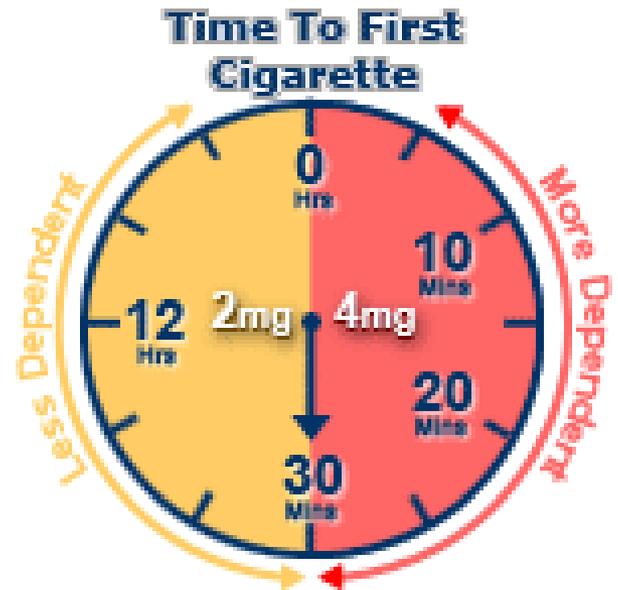


Use Commit® Lozenge 2mg:
if you smoke your first
cigarette more than 30
minutes after waking up

4
mg



Use Commit® Lozenge 4mg:
if you smoke your first
cigarette of the day within
30 minutes of waking up





Choose **Commif®** Lozenge if you:

- Smoke at irregular intervals (e.g., more in the evening)
- Want to control your nicotine intake
- Need to keep your mouth busy
- Prefer not to or cannot chew gum

Choose **NicoDerm® CQ®** patch if you:

- Smoke at regular intervals (e.g., every half hour)
- Prefer not to take oral medication

Choose **Nicorette®** gum if you:

- Smoke at irregular intervals (e.g., more in the evening)
- Want to control your nicotine intake
- Want to chew or occupy your mouth

Advantages Include:

- Fast, convenient — fits easily in your pocket or purse
- Practically unnoticeable
- Easy-to-follow tapered dosing (to gradually reduce the number of lozenges used)

- Once-a-day application
- Available in Clear Patch: the first and only one
- Step-down dosing
- Flexibility of 24-hour or 16-hour use

- Oral gratification
- Convenience — use anytime, anywhere
- Control over how much you use and when

Save on Your Product of Choice:



Now You Can Beat Cigarettes with Your Own Two Hands

If you're the kind of smoker who feels a bit anxious without a cigarette in your hands, the Nicotrol Inhaler may be right for you.

In a survey, 41% of smokers said that one of the reasons their last quit attempt failed was because they missed the hand-to-mouth gratification they've come to depend on after years of smoking.

Nicotrol Inhaler:

- 4-20 cartridges/day used for 3 months then discontinued:

Quit Rates by Treatment (N= 445 Patients in 2 Studies)					
Group	Number of Patients	At 6 Weeks	At 3 Months	At 6 Months	At 12 Months
Nicotrol Inhaler	223	44-45%	31-32%	20-21%	11-13%
Placebo	222	14-23%	8-15%	6-11%	5-10%

Patients who used NICOTROL Inhaler had a significant reduction in the "urge to smoke", a major nicotine withdrawal symptom, compared with placebo- treated patients throughout the first week,



How to use the cartridge:

- NICOTROL[®] Inhaler (nicotine inhalation system) consists of a mouthpiece and a plastic cartridge delivering 4 mg of nicotine from a porous plug containing 10 mg nicotine. The cartridge is inserted into the mouthpiece prior to use.
- An intensive inhalation regimen (80 deep inhalations over 20 minutes) releases on the average 4 mg of the nicotine content of each cartridge of which about 2 mg is systemically absorbed.

Nose Spray Kinetics:



Figure 1: Mean and Range of the 95th and 5th Percentile Nicotine Concentrations After a 1 mg Dose of NICOTROL NS (n=30).

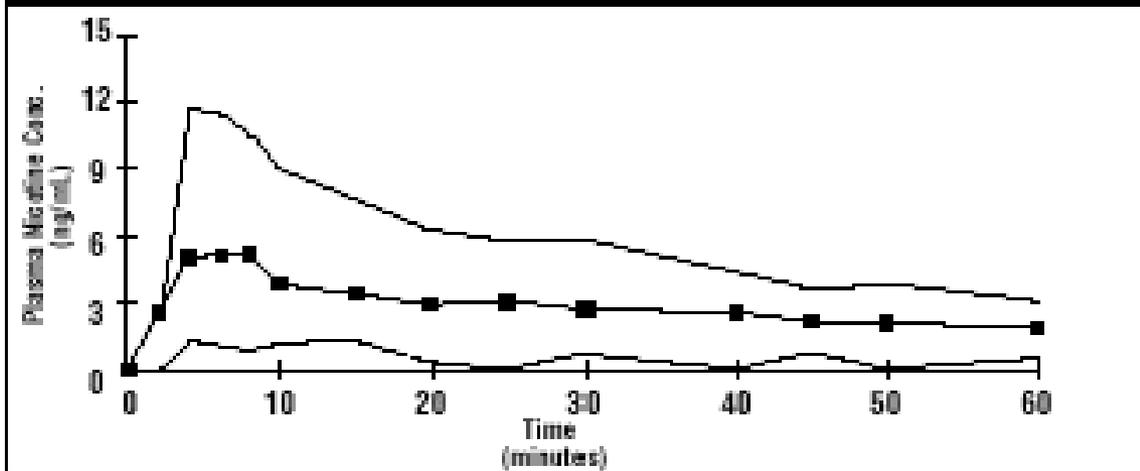


Table 1: Trough Plasma Nicotine Concentrations after 11 Hours of Dosing With 1 mg, 2 mg and 3 mg of NICOTROL NS per hour (n=16).

Dose	Mean (ng/mL) \pm SD	(Range)
1 mg every 60 minutes (1 mg/hr)	8 \pm 3	(1.7-12)
1 mg every 30 minutes (2 mg/hr)	14 \pm 6	(1.5-24)
1 mg every 20 minutes (3 mg/hr)	18 \pm 10	(1.2-35)

Nicotrol Nose Spray: Efficacy:

- 3 months, minimum of 8 mg maximum 40 mg of nicotine a day
- Quitting defined as no cigs for 4 weeks
- Use allowed for 6 months or to 1 year
 - No difference on extended efficacy



Table 3: Quit Rates by Treatment (N=730 smokers in 3 Studies)

Group	Size (n)	At 6 Weeks	At 3 Months	At 6 Months	At 1 Year
NICOTROL NS	369	49–58%	41–45%	31–35%	23–27%
Placebo	361	21–32%	17–20%	12–15%	10–15%

How to use the NS:

- Nicotrol[®] NS (nicotine nasal spray) is an aqueous solution of nicotine intended for administration as a metered spray to the nasal mucosa. Nicotine is a tertiary amine composed of pyridine and a pyrrolidine ring.
- Each actuation of NICOTROL NS delivers a metered 50 microliter spray containing approximately 0.5 mg of nicotine. One dose is considered 1 mg of nicotine (2 sprays, one in each nostril).

- **Myth #9:**
 - The nicotine patch and gum should not be used at the same time and/or in combination with bupropion.
- **Fact:**
 - The nicotine patch and gum may be used at the same time and/or in combination with bupropion.

Adjunctive Therapy:

- Bupropion Hydrochloride: Zyban
- 150 x 3 days, 150 BID for 8 weeks



Table 1. Dose-Response Trial: Quit Rates by Treatment Group

Abstinence From Week 4 Through Specified Week	Treatment Groups			
	Placebo (n = 151) % (95% CI)	ZYBAN 100 mg/day (n = 153) % (95% CI)	ZYBAN 150 mg/day (n = 153) % (95% CI)	ZYBAN 300 mg/day (n = 156) % (95% CI)
Week 7 (4-week quit)	17% (11-23)	22% (15-28)	27%* (20-35)	36%* (28-43)
Week 12	14% (8-19)	20% (13-26)	20% (14-27)	25%* (18-32)
Week 26	11% (6-16)	16% (11-22)	18% (12-24)	19%* (13-25)

* Significantly different from placebo ($p \leq 0.05$).

How to start: Bupropion

- 1 week before set quit date
- 150 mg once a day in am for 3 days
 - decreases the CNS stimulation SE
- 150 mg BID for 4 days
- Then stop cigs

What is the BEST:

- NRT PLUS Bupropion for 9 weeks
- Patch tapered at week 8 to 14, week 9 to 7 mg

Table 2. Comparative Trial: Quit Rates by Treatment Group

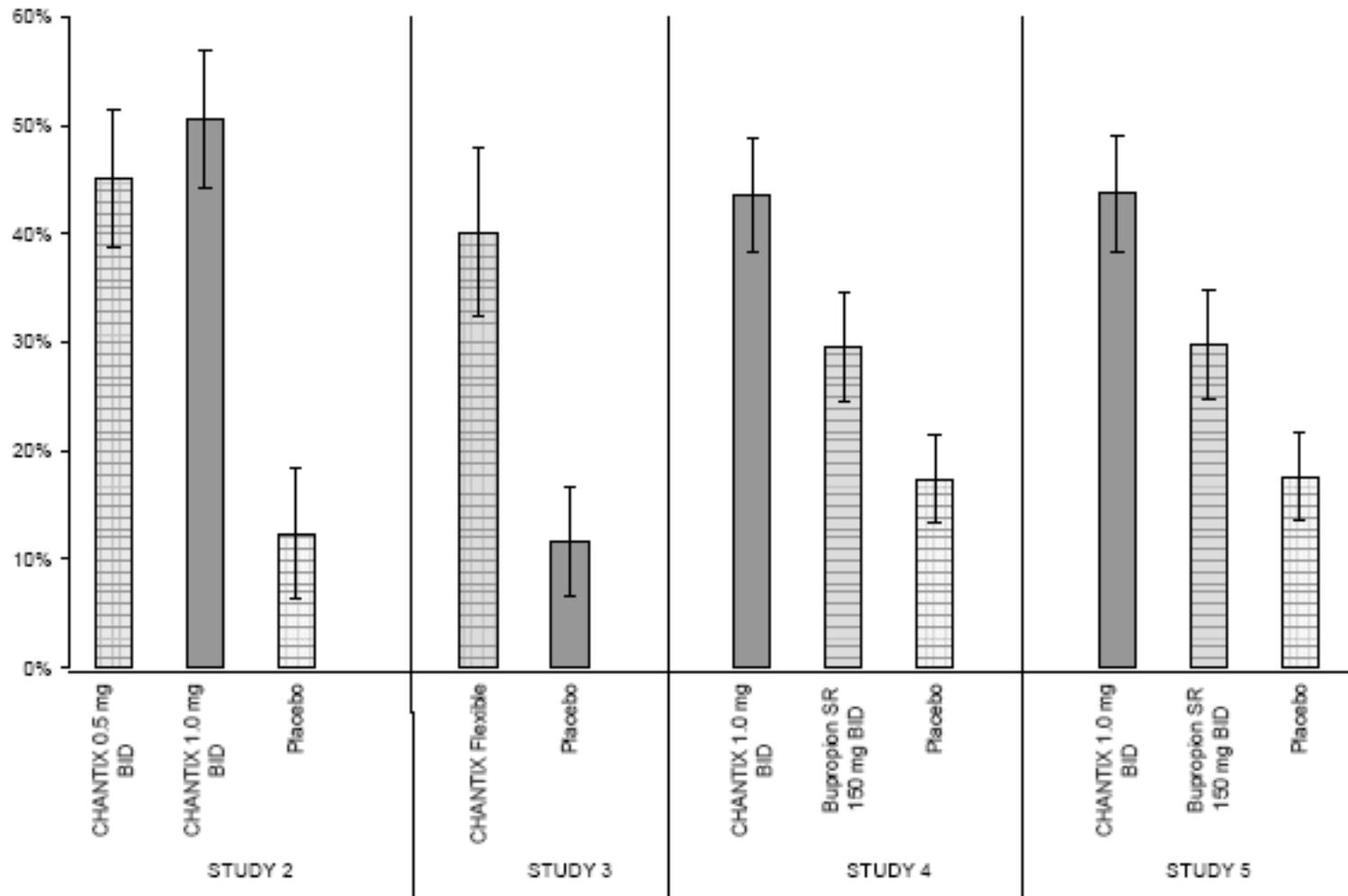
Abstinence From Week 4 Through Specified Week	Treatment Groups			
	Placebo (n = 160) % (95% CI)	Nicotine Transdermal System (NTS) 21 mg/day (n = 244) % (95% CI)	ZYBAN 300 mg/day (n = 244) % (95% CI)	ZYBAN 300 mg/day and NTS 21 mg/day (n = 245) % (95% CI)
Week 7 (4-week quit)	23% (17-30)	36% (30-42)	49% (43-56)	58% (51-64)
Week 10	20% (14-26)	32% (26-37)	46% (39-52)	51% (45-58)

However,

- Abstinence at 1 year out was not statistically different in the combo treatment group as the bupropion treatment group
 - 28 percent in the combo
 - 23% in Zyban
 - 8% placebo

Varenicline Chantix[®] Efficacy:

Figure 1: Continuous Abstinence, Weeks 9 through 12



Varenicline Chantix® Long Term

Figure 2: Continuous Abstinence, Weeks 9 through 52

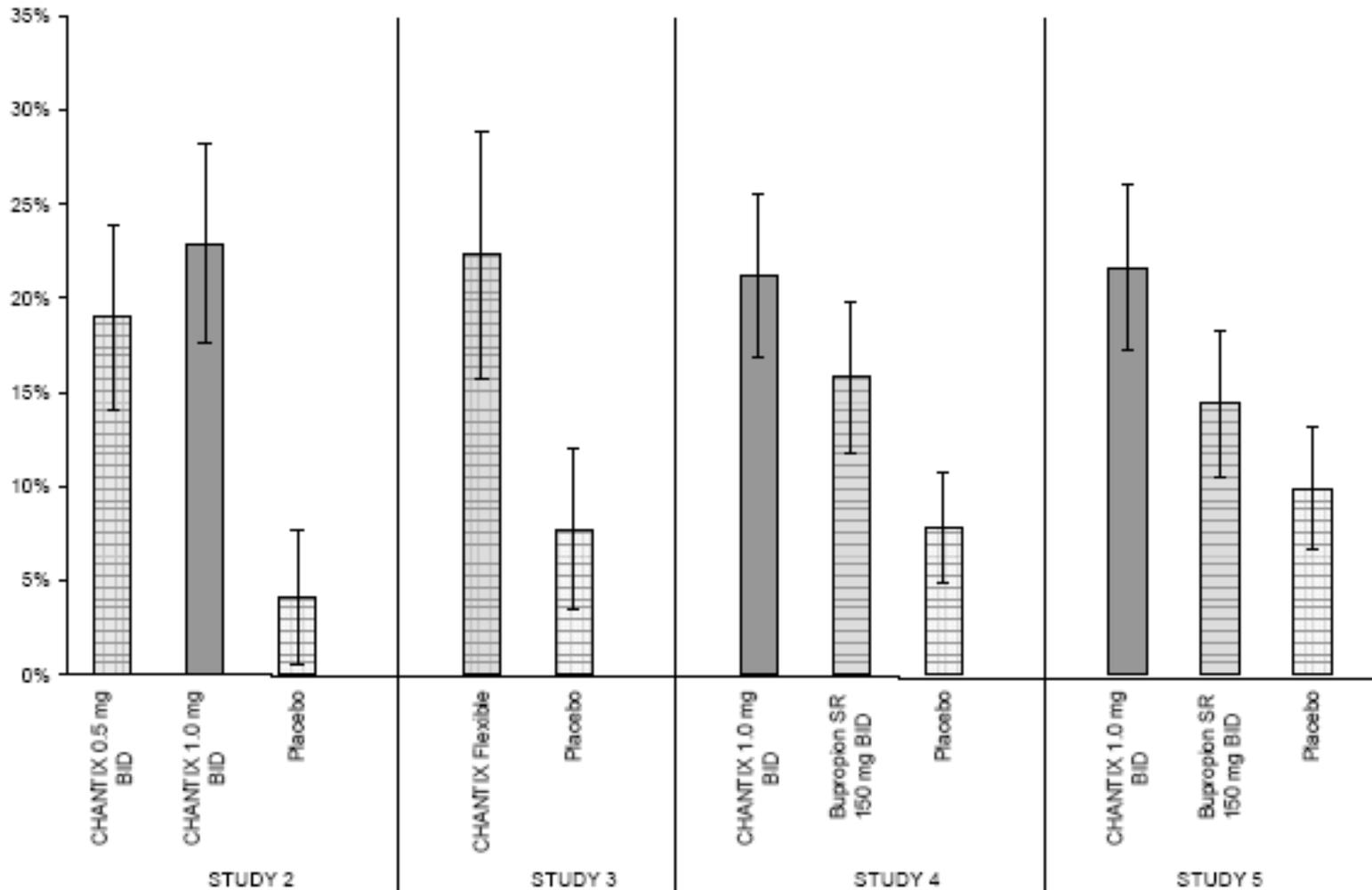


Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies ($\geq 1\%$ in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1 mg BID N=821	Placebo N=805
GASTROINTESTINAL			
GI Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain *	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4
PSYCHIATRIC DISORDERS			
Sleep Disorder/Disturbances			
Insomnia **	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
NERVOUS SYSTEM			
Headaches			
Headache	19	15	13

Varenicline Chantix®

- Starter Month:
 - 0.5 mg a day for 3 days
 - 0.5 mg BID for days 4-7
 - 1.0 mg BID
- Continued for 12 weeks
 - If not smoking- continue for 12 weeks
 - If smoking- encourage another attempt to stop



Warning Chantix® 2/1/08

Public Health Advisory Important Information on Chantix (varenicline)

FDA is issuing this public health advisory to alert patients, caregivers, and healthcare professionals to important changes to Chantix prescribing information. Chantix is a medicine used to help patients stop smoking.

At the request of FDA, Pfizer, the manufacturer of Chantix, has updated the Chantix prescribing information to include warnings about the possibility of severe changes in mood and behavior in patients taking Chantix. FDA is highlighting the following related important safety information on Chantix:

- **Patients should tell their doctor about any history of psychiatric illness prior to starting Chantix.** Chantix may cause worsening of a current psychiatric illness even if it is currently under control and may cause an old psychiatric illness to reoccur.
- **Healthcare professionals, patients, patients' families, and caregivers should be alert to and monitor for changes in mood and behavior in patients treated with Chantix.** Symptoms may include anxiety, nervousness, tension, depressed mood, unusual behaviors and thinking about or attempting suicide. **In most cases, neuropsychiatric symptoms developed during Chantix treatment, but in others, symptoms developed following withdrawal of varenicline therapy.**
- **Patients taking Chantix should immediately report changes in mood and behavior to their doctor.**
- **Patients taking Chantix may experience vivid, unusual, or strange dreams.**
- **Patients taking Chantix may experience impairment of the ability to drive or operate heavy machinery.**

While Chantix has demonstrated clear evidence of efficacy, it is important to consider these safety concerns and alert patients that they are possible.

What are patients hearing?

- Passionflower helps promote calm, security and normal sleep.
- Eleuthero fosters relaxation to counteract the effects of physical and emotional stress.
- Bayberry Root helps maintain a healthy immune system.
- Echinacea Powder stimulates a feeling of well being and contentment.
- Ginseng- Fosters relaxation, to counteract the effects of physical and emotional stress.
- You have to eliminate the nicotine from your body!
- Nicotine residue actually triggers your body to want more of it.
- Smoke Away works to literally wipe all traces of nicotine from your body with its all-natural ingredients.
- Burdock Root cleanses your body of nicotine deposits.
- Golden Seal Root cleanses your digestive tract of all traces of tobacco and nicotine.
- Bayberry Root helps maintain a healthy immune system.
- Hyssop cleanses your lungs,relieves congestion .



FORMULA 1 Ingredients:

Lobelia Powder, Licorice Root Powder, Passion Flower Powder, Sarsparilla Root Power, Siberian Ginseng Powder, Echinacea Purpurea Herb, Elderberry Extract, Ginger Root Powder, Barley Grass Powder, Bayberry Root Powder, Cayenne Pepper, Lemon Grass Powder, Peppermint Powder, Safflower Powder, Piper Langum Powder, Bioperene Powder, Burdock Root Powder, Golden Seal Powder, Oregon Grape Powder, Oxbile Powder, Alfalfa Herb Powder, Buckthorn Bark Powder, Cascara Sagrada Powder, Dandelion Root Powder, Hyssop Leaf Powder.



Medication Cost:



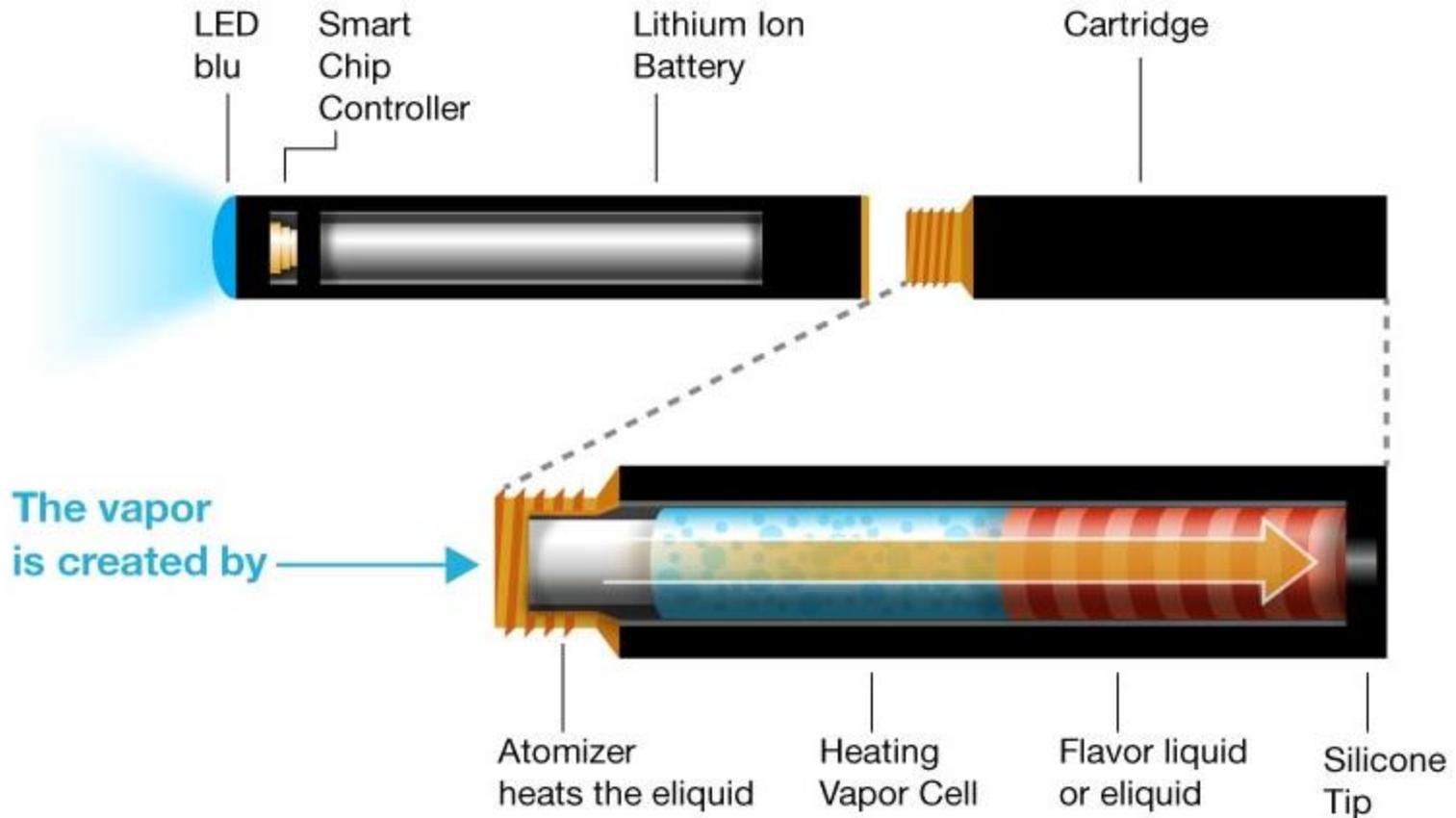
- Nicorette Gum: otc
 - 2 mg/110 “Starter pack”- \$48.01, #48-26.41
 - 4 mg/110 “starter pack”- \$52.01, #48- 29.11
- Nicotrol NS: RX 2013
 - \$272.01 AWP 4 x 10 ml
- Nicotrol Inhaler: RX
 - \$272.01- AWP 168 10 mg cannisters
- Nicoderm CQ otc
 - \$29-53.01/14 days- 21, 14, 7 mg strength
- Nicotrol step 1-3 Otc
 - \$46.00- 14 days
- Bupropion Zyban[®]
 - \$223.00/ month- Brand
 - Wellbutrin[®] -
 - Generics
 - BID 150 tablet-
 - Around \$30.00

“Vaping”

- **eCig (Vaping) vs Analog (Tobacco) Cigarettes**
- **USA Sales estimated between 1.5-2.5 Billion!**
- **Tripled over 2012!!**
- **Estimated to have $\frac{1}{4}$ - $\frac{1}{2}$ the “Users” Market 5 years**
- **Various Strengths Nicotine, Flavors**
- **Disposable devices vs rechargeable, refillable**
- **Manufacturers say “Safer”**
- **FDA says “hold your horses”**

Electronic Cigarettes

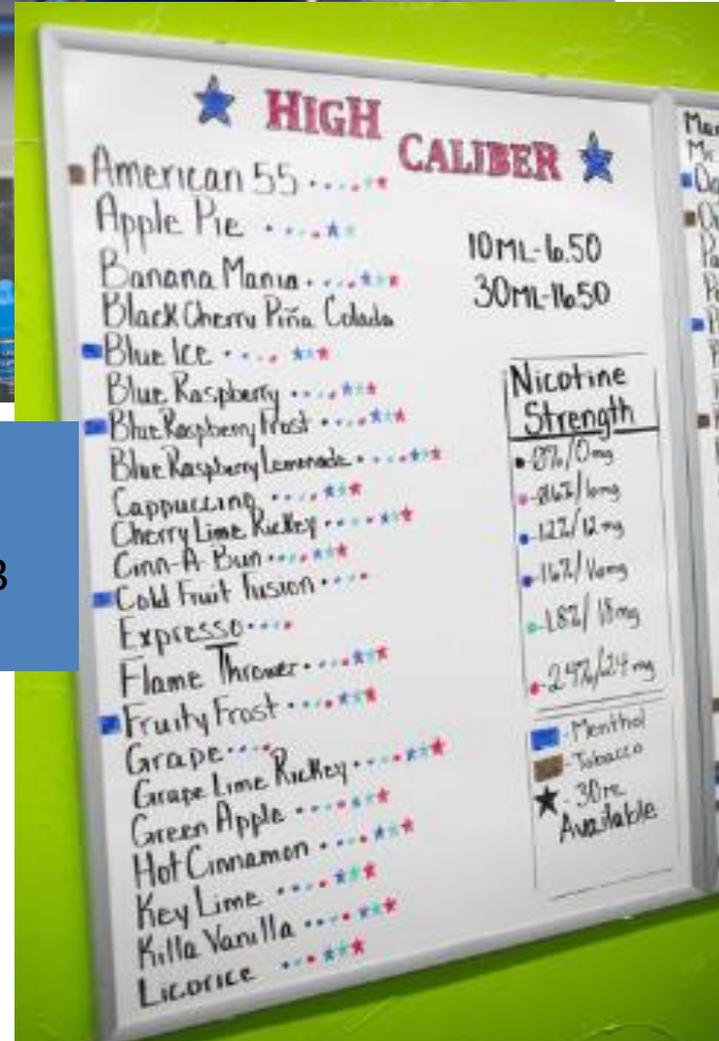
Inside of Electronic Cigarette





Idaho Statesman
 Business Insider
 November 5-11th 2013
 Photos by Kyle Green

Volt Vapes and
 ElectroNicStix



Has it been studied for NRT and Smoking Cessation?

- YES!
- And we will have LOTS of data in the next few years
- Bullen, McRobbie, Thornley- Effect of an electronic nicotine deliver device on desire to smoke and withdrawal, user preference and nicotine delivery.
- Dawkins, Turner, Hasna- The electronic-cigarette- Effects on desire to smoke, withdrawal symptoms and cognition.
- Polosa, Caponeeto, Morjaria- Effects of an electronic nicotine delivery devise on smoking reduction and cessation- a prospective 6 month pilot study.
- Etc.

RESEARCH ARTICLE

Open Access

Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study

Riccardo Polosa^{1,2*}, Pasquale Caponnetto^{1,2}, Jaymin B Morjaria³, Gabriella Papale^{1,2}, Davide Campagna^{1,2} and Cristina Russo^{1,2}

- 40 Patients, Not desiring to quit, Pilot Study
- 5 visits, baseline, weeks 4, 8, 12, 24
- Product use, Number of cigarettes smoked and carbon monoxide levels measured at each visit
- 7.5 mg “Original” Categoria e-Cigarettes provided (Italian)
- Primary outcome- “Reducers” 50% reduction cigs
- Secondary efficacy “Heavy Reducers” 80% reduction cigs
- Secondary efficacy “Quitters” – abstinence from tobacco smoke
- Adverse events, and product preference evaluated

Results: Cig Reduction

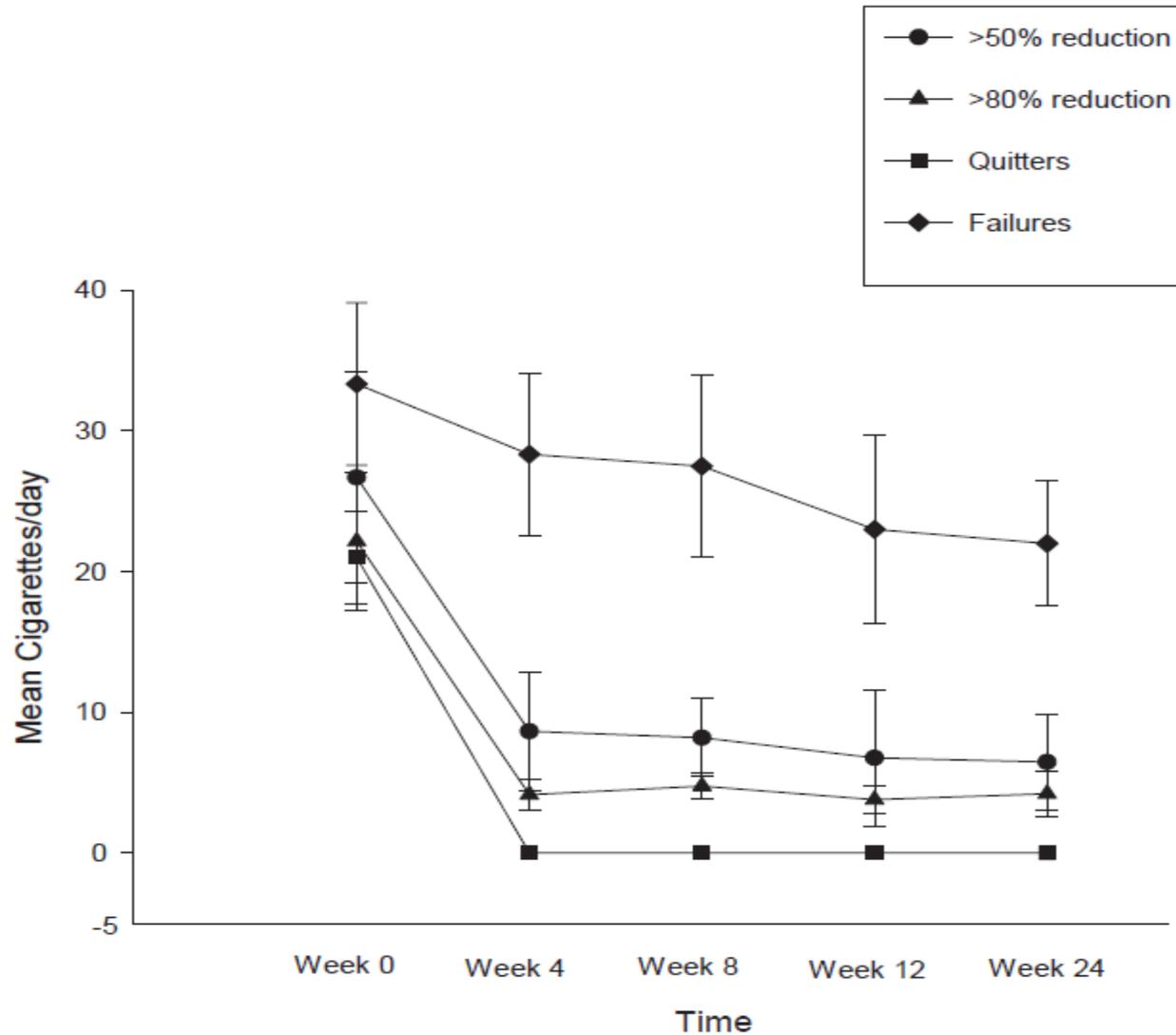
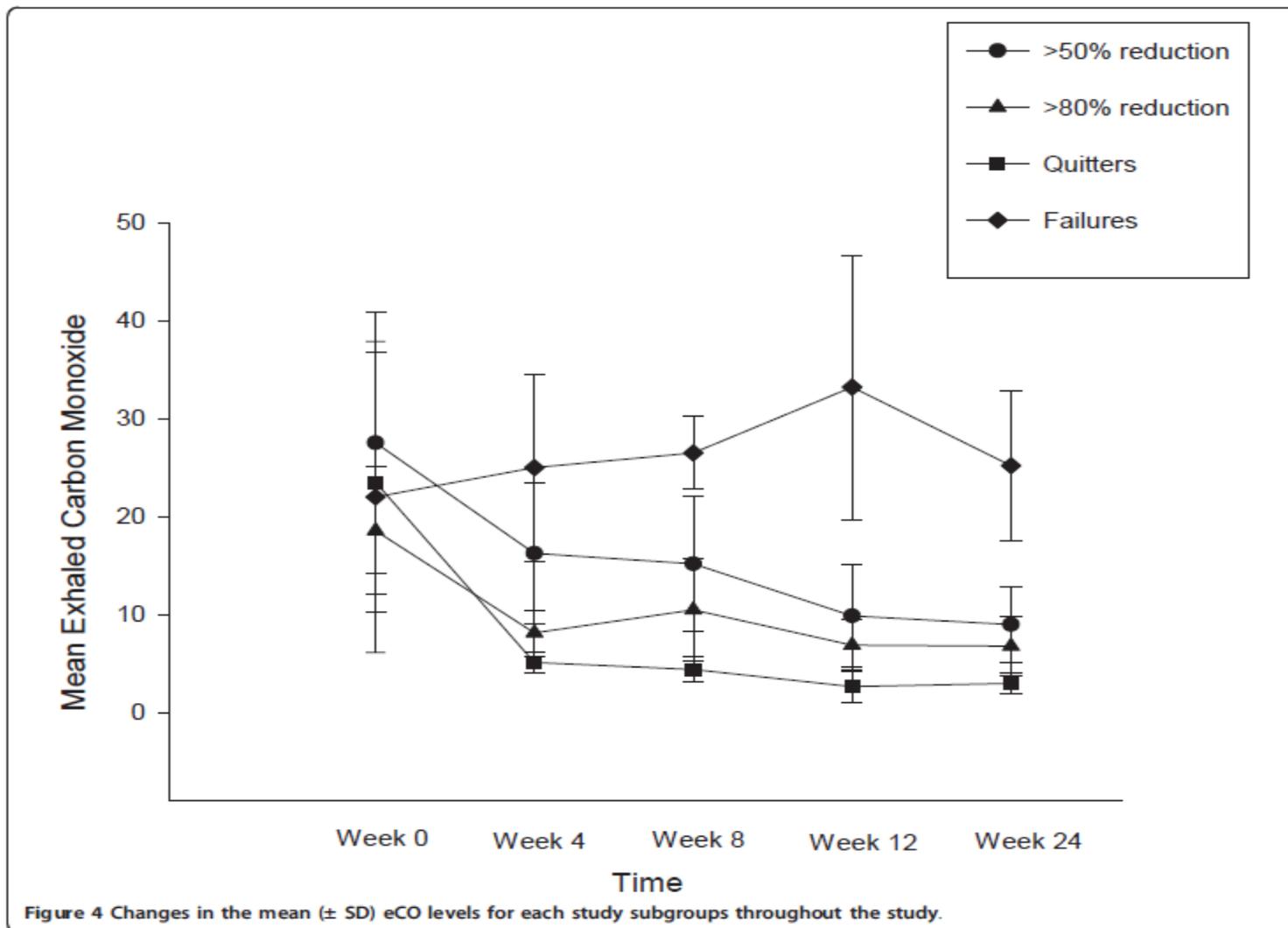
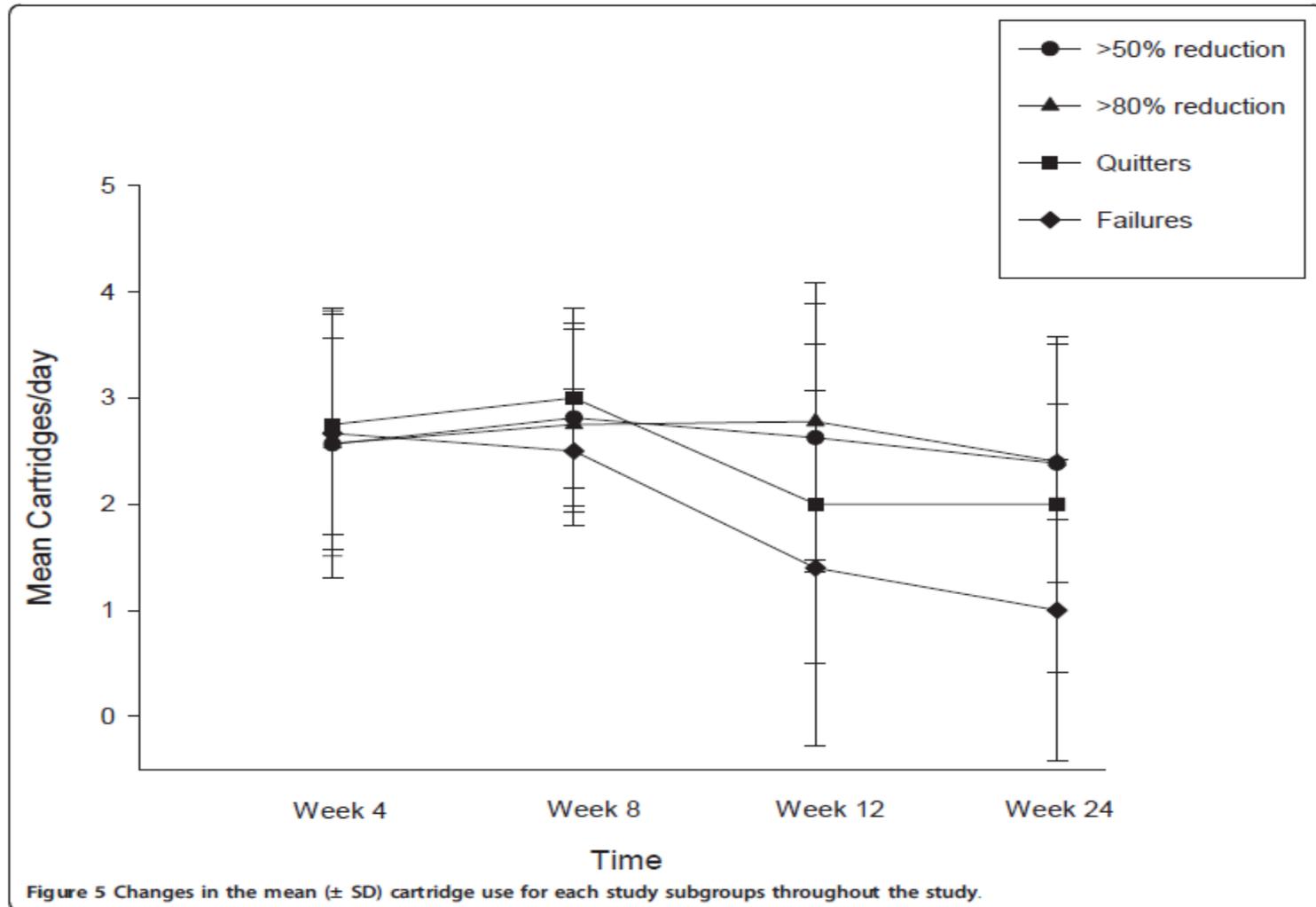


Figure 3 Changes in the mean (\pm SD) cigarette use for each study subgroups throughout the study.

Results: Exhaled Carbon Monoxide



Results: Mean Cartridges/day



Results/Adverse Events/Discussion

Table 3 Adverse events reported by participants who completed all study visits

Adverse Event	Study Visits			
	4-week n/n (%)	8-week n/n (%)	12-week n/n (%)	24-week n/n (%)
Throat irritation*	11/34 (32,4%)	5/32 (15,6%)	5/30 (16,7%)	4/27 (14,8%)
Mouth Irritation*	7/34 (20,6%)	4/32 (12,5%)	3/30 (10,0%)	2/27 (7,4%)
Sore Throat	4/34 (11,8%)	1/32 (3,1%)	1/30 (3,3%)	0/27 (0,0%)
Dry cough	11/34 (32,4%)	6/32 (18,8%)	3/30 (10,0%)	3/27 (11,1%)
Dry mouth	3/34 (8,8%)	1/32 (3,1%)	1/30 (3,3%)	1/27 (3,7%)
Mouth ulcers	1/34 (2,9%)	1/32 (3,1%)	1/30 (3,3%)	0/27 (0,0%)
Dizziness [§]	5/34 (14,7%)	2/32 (6,3%)	2/30 (6,7%)	1/27 (3,7%)
Headache	4/34 (11,8%)	2/32 (6,3%)	2/30 (6,7%)	1/27 (3,7%)
Nausea	5/34 (14,7%)	2/32 (6,3%)	1/30 (3,3%)	1/27 (3,7%)

* Throat and mouth irritation were described either as tickling, itching, or burning sensation

[§] Dizziness, was also used to mean vertigo and light-headedness.

- 50% Reduction
 - 13/40 (32.5%)
- 80% Reduction
 - 5/40 (12.5%)
- Smoking Abstinence
 - 9/40 (22.5%)
 - 6/9 still using e-cig
- “use of e-Cig substantially decreased cigarette consumption without significant side effects in smokers not intending to quit”

The others:

- Showed very similar results
- Future:
- [<http://clinicaltrials.gov/ct2/show/NCT01164072?term=electronic+cigarette&rank=1>].
- [<http://clinicaltrials.gov/ct2/show/NCT01194583?term=polosa&rank=2>]
- [<http://clinicaltrials.gov/ct2/show/NCT01188239?term=polosa&rank=3>].
- [http://www.anzctr.org.au/trial_view.aspx?ID=336091].
- Plus Many Many more

The End

- Do we want a
- “Tobacco Free Idaho”
– or a
- “Nicotine Free Idaho”
- Questions?
- Let the debate begin

