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Varenicline and Other Pharmacotherapies for Tobacco Dependence

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Learning Objectives

- Understand the mechanism of action for novel therapeutics for tobacco dependence
- Describe the evidence supporting the efficacy for newer drug treatments
- Understand safety issues for varenicline
- Know how to prescribe varenicline

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Presentation Outline

- Background on new drug development
- Review of evidence for varenicline efficacy
  - Phase 2 clinical trials
  - Phase 3 pivotal trials
  - Other clinical trial evidence
- Review varenicline safety and prescribing
- Review investigational new drugs for tobacco dependence

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Abstinence: The Effects of Treatment*

• Spontaneous	1-2%
• Advice to quit	3-5%
• Advice plus NRT	6-12%
• Counseling + Rx#	15-20%
• Clinical trials	20-25%
• Residential treatment	45-50%

* 12 month abstinence rates; # Rx= tailored pharmacotherapy

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History of Pharmacotherapy

- Nicotine polacrilex (gum) 1982
- Nicotine patch 1992
- Nicotine patch and gum OTC 1996
- Bupropion SR 1997
- Nicotine lozenge OTC 2002
- Varenicline 2006

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Need for New Therapy

- Long-term abstinence disappointingly low
- Current therapy available 10-20 years
- New therapeutic options may motivate hardened smokers
- New therapeutic targets to be exploited

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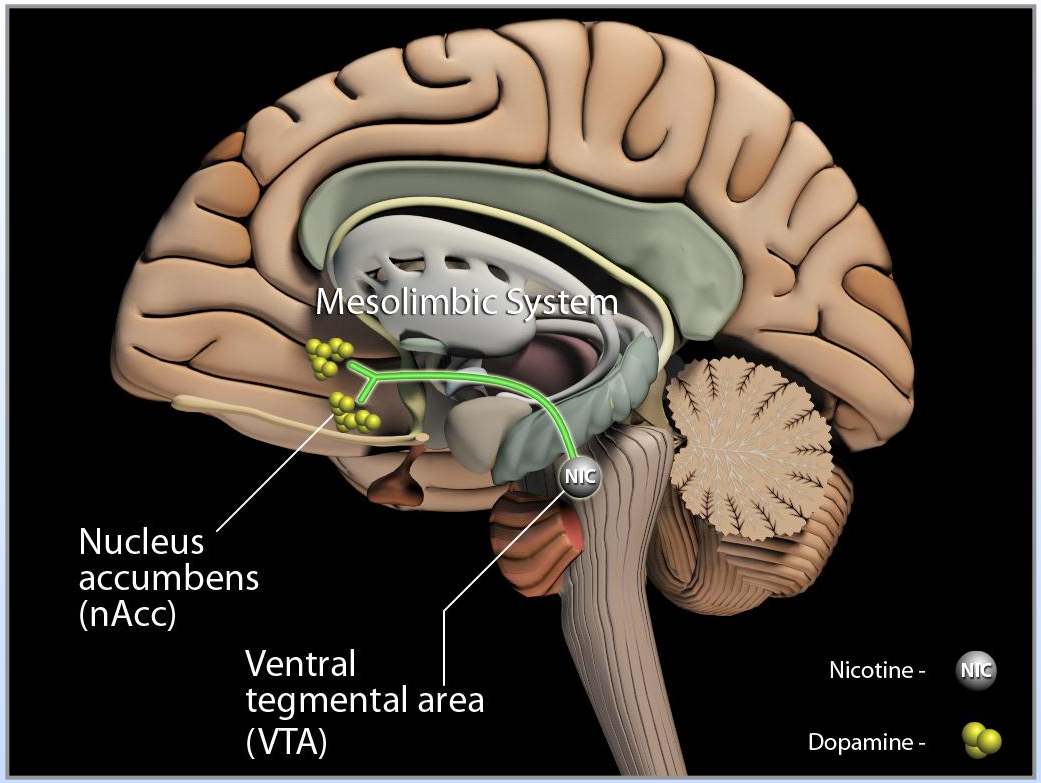
Central Nervous System “Reward Center”



Dopamine (DA) release in the nucleus accumbens is thought to be the “final common pathway” for the rewarding effects of most drugs of abuse

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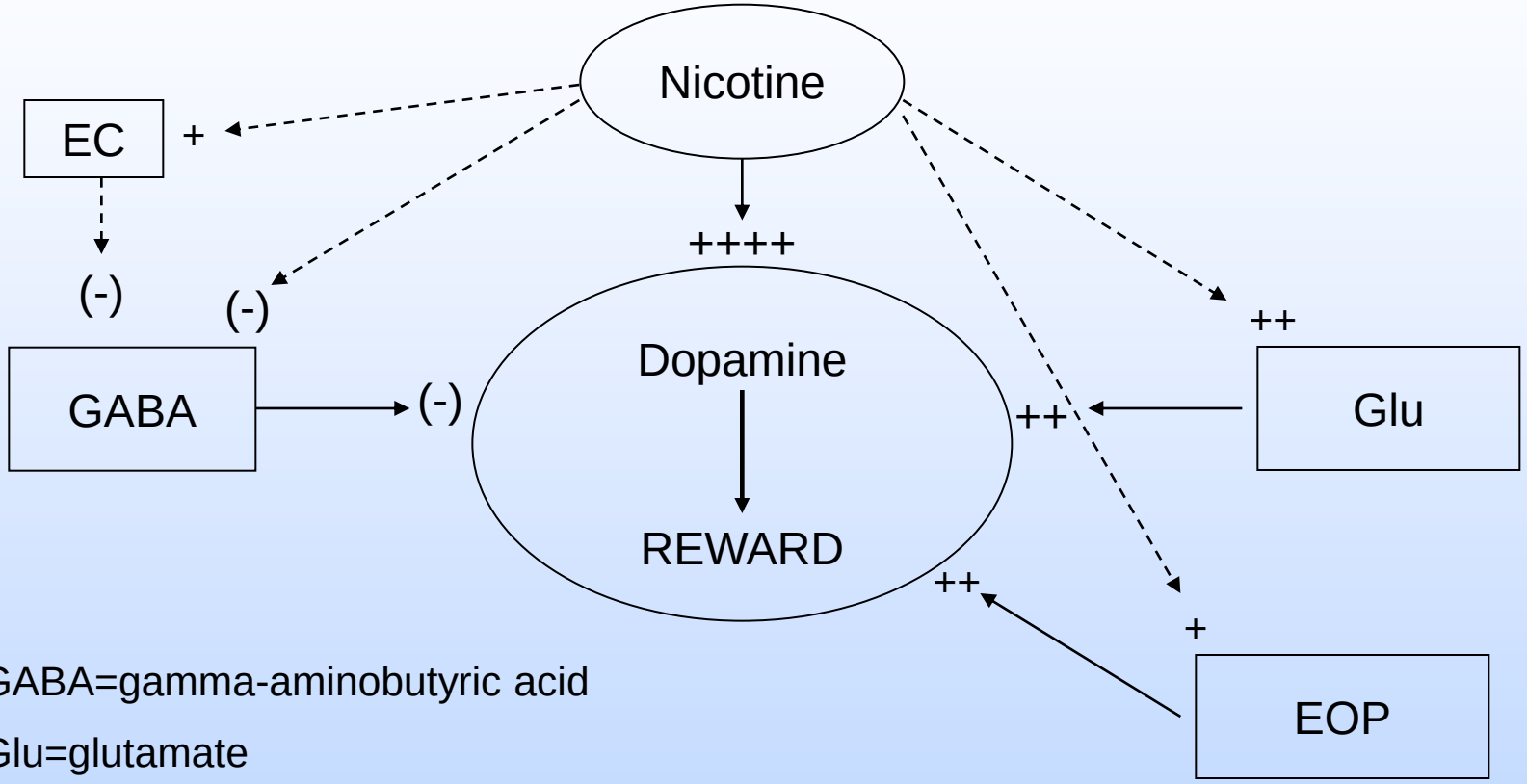
Nicotine: Multiple Pathways to Reward



GABA=gamma-aminobutyric acid

Glu=glutamate

EC=endocannabinoids

EOP=endogenous opioid peptides

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Pathways to Alter Nicotine Reward

- GABA and Glutamate
  - Topiramate
  - Gabapentin
  - Acamprosate
- Endocannabanoid-1 receptor blocker
  - Rimonabant
- Opioid receptor antagonist
  - Naltrexone

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The nAChR

- Pentameric receptors throughout the brain and composed of alpha and beta subunits
- Highest concentration of nAChR's is in the mesolimbic dopaminergic system ("reward center")
- The high affinity nAChR is the α4β2
- Stimulation of the α4β2 nAChR causes DA release in the reward center

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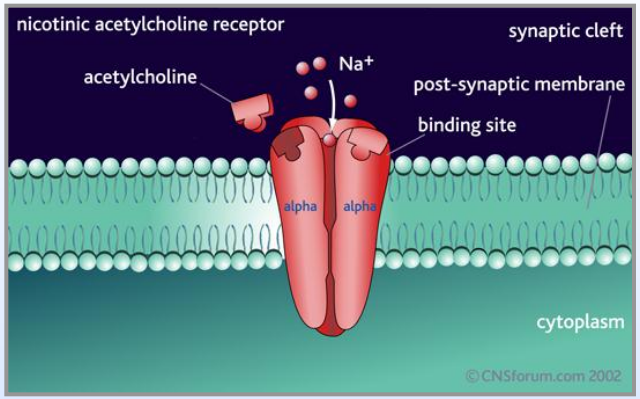
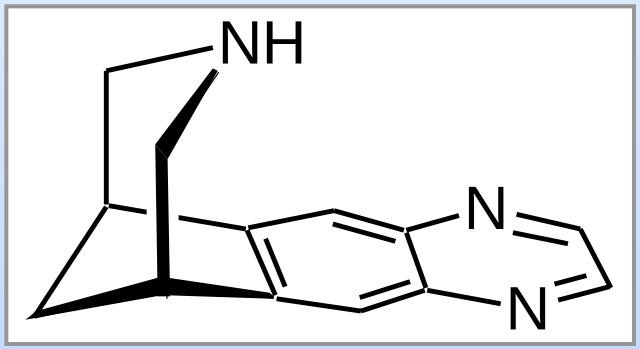
Varenicline Mechanism of Action

- Varenicline targets the nicotinic acetylcholine receptor (nAChR) in a unique fashion
- Partial agonist with specificity for the high-affininty α4β2 nAChR
- Agonist -- stimulates the receptor to decrease craving and withdrawal
- Antagonist—blocks the receptor to decrease the reinforcement associated with smoking
- No clinically relevant drug-drug interactions





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Phase 2 Trials

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Dose-Ranging Study

- 5-arm study comparing…
  - Varenicline 0.3 mg daily
  - Varenicline 1.0 mg daily
  - Varenicline 1.0 mg twice daily
  - Bupropion SR 150 mg twice daily
  - Placebo
- Active treatment for 7 weeks
- Follow-up for 12 months
- Main outcome abstinence from week 4

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Dose-Ranging Study Results (% Abstinent)

Treatment (N=638)	Week 4-7	Week 4-24	Week 4-52
Var 0.3/d	25.4	9.5	7.9
Var 1.0/d	31	9.5	5.6
Var 1.0 bid	40.8	20.8*	14.4*
BupSR	28.6	10.3	6.3
Placebo	13.8	7.3	4.9

*P≤0.01; all other week 24 and 52 comparisons P=NS

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Titration Study

- 5-arm study comparing 2 doses and initial ramp-up (titrated) vs. no ramp-up (non-titrated)
  - Varenicline 0.5 mg BID titrated
  - Varenicline 0.5 mg BID non-titrated
  - Varenicline 1.0 mg BID titrated
  - Varenicline 1.0 mg BID non-titrated
  - Placebo
- Compare abstinence weeks 9-12 and 9-52
- Compare frequency of adverse events

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Titration Study Results (% Abstinent)

Treatment (N=647)	Weeks 9-12	Weeks 9-52
Var 0.5 mg BID Titrated	40.8	18.5
Var 0.5 mg BID Non-titrated	47.3	18.6
Var 1.0 mg BID Titrated	54.6	25.4
Var 1.0 mg BID Non-titrated	44.2	19.4
Placebo	11.6	3.9

Oncken et al. Arch Intern Med 2006;166:1571-1577

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Self-Titration (Flexible Dosing) Study

- RCT of 320 subjects Varenicline 1 mg BID vs. placebo for 12 weeks
- After usual titration week subjects could self-regulate dose between Varenicline 0.5 mg/ day and 1.0 mg BID
- Varenicline was superior to placebo at all comparisons
- Mean modal dose of varenicline was 1.35 mg per day
- Nausea was less common (13.4% varenicline vs 5.2% placebo) compared to other studies
- Trend toward tapering dose of varenicline over time

Niaura et al. Current Medical Research & Opinion. 2008;24:1931-41

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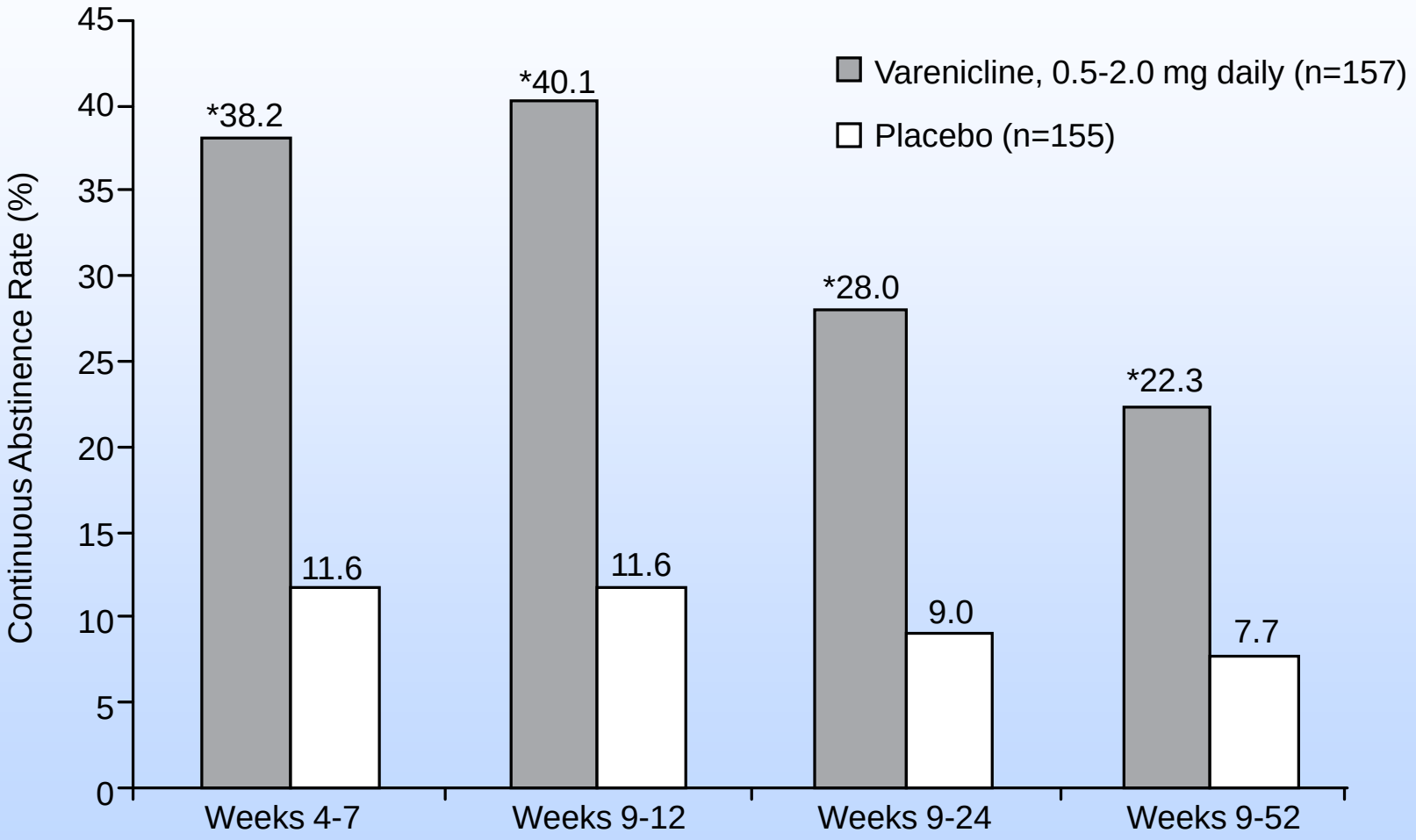
Flexible Dosing Prolonged Abstinence



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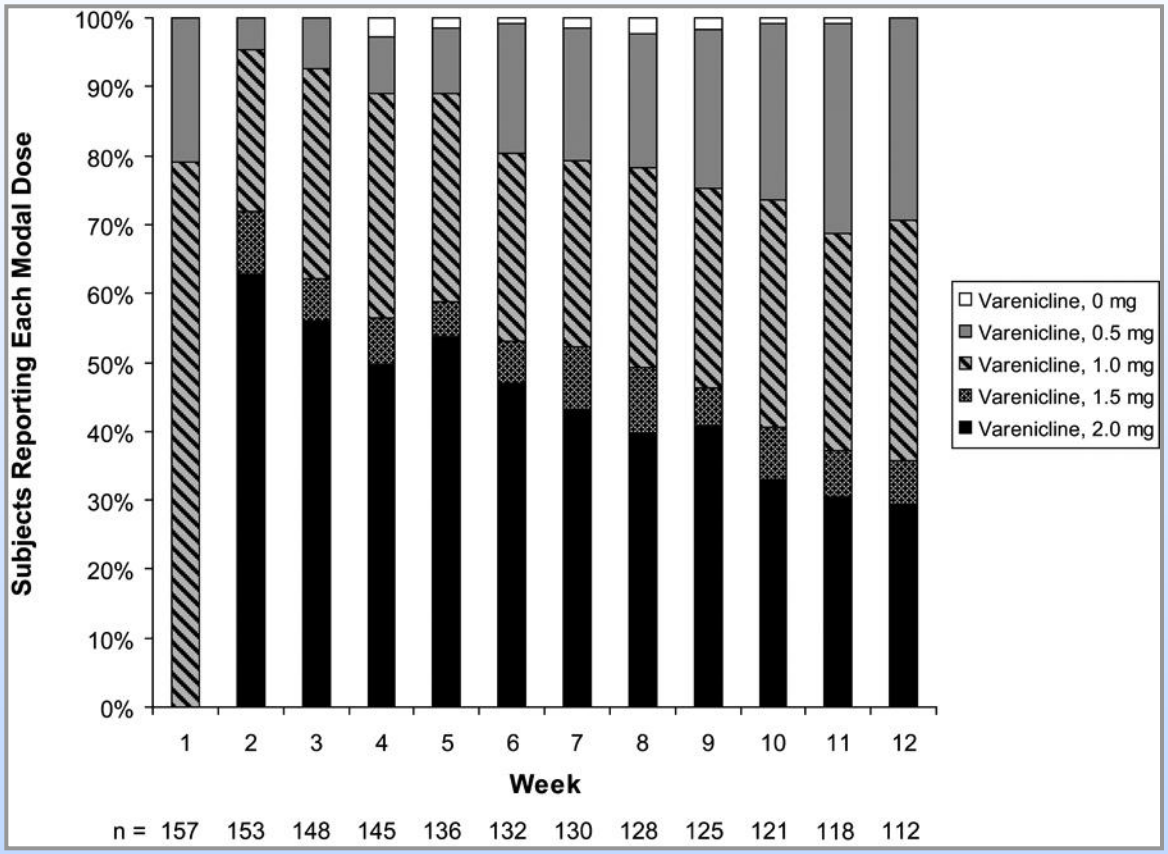
Self-Titration (Flexible Dosing) Study

Varenicline: Mean-modal dose



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Conclusions from Varenicline Phase 2 Trials

- Most efficacious dose is 1 mg twice daily
- There is a dose response from 0.5 mg per day to 2 mg per day
- Initial dose titration (ramp-up) reduces nausea compared with non-titration
- “Self-titration” may be an alternative to fixed dose approach

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Phase 3 Trials

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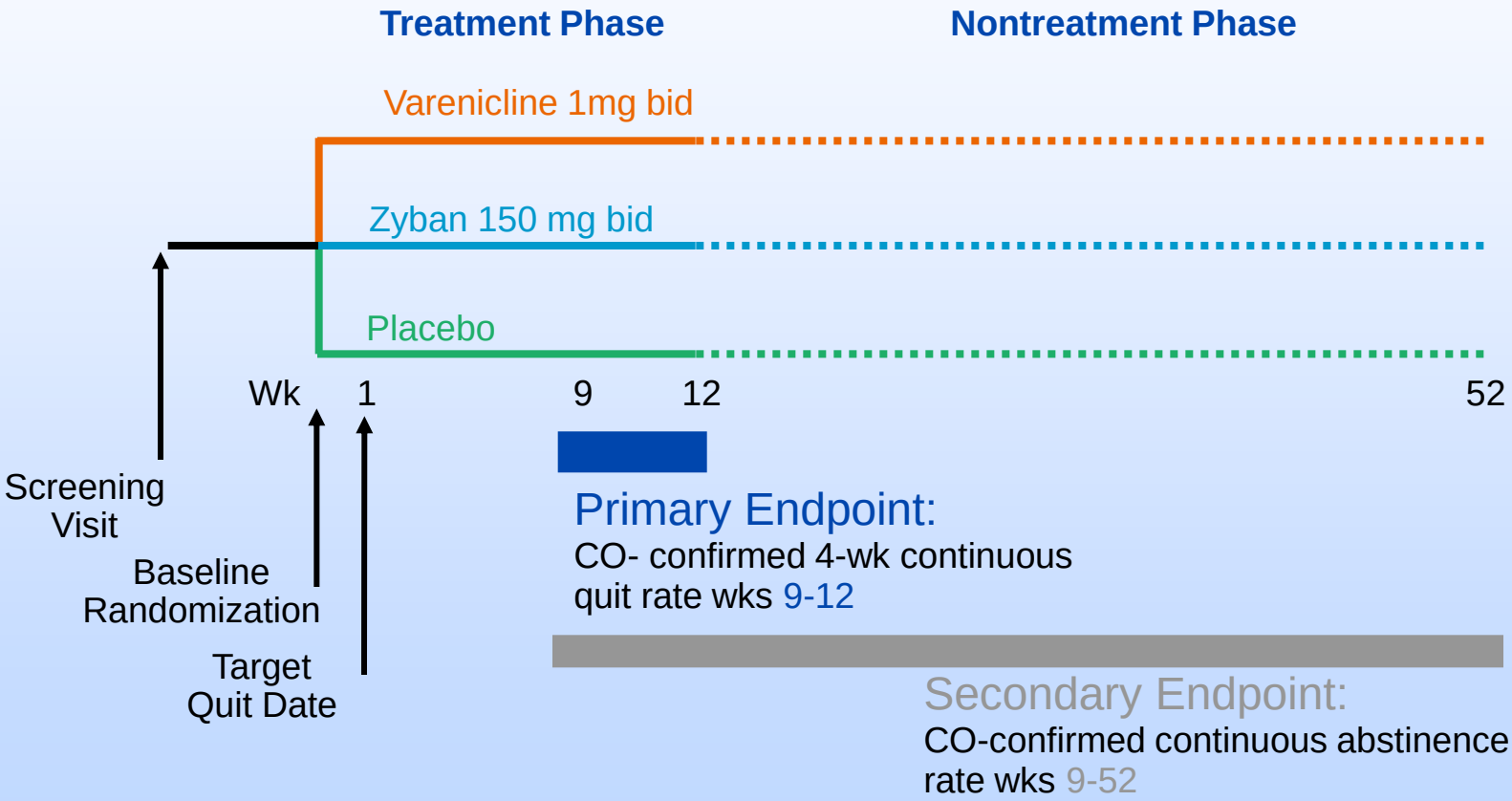
Varenicline Pivotal Trials Design

Subjects are 18-75 yr old, Zyban naïve, average ≥10 CPD past year



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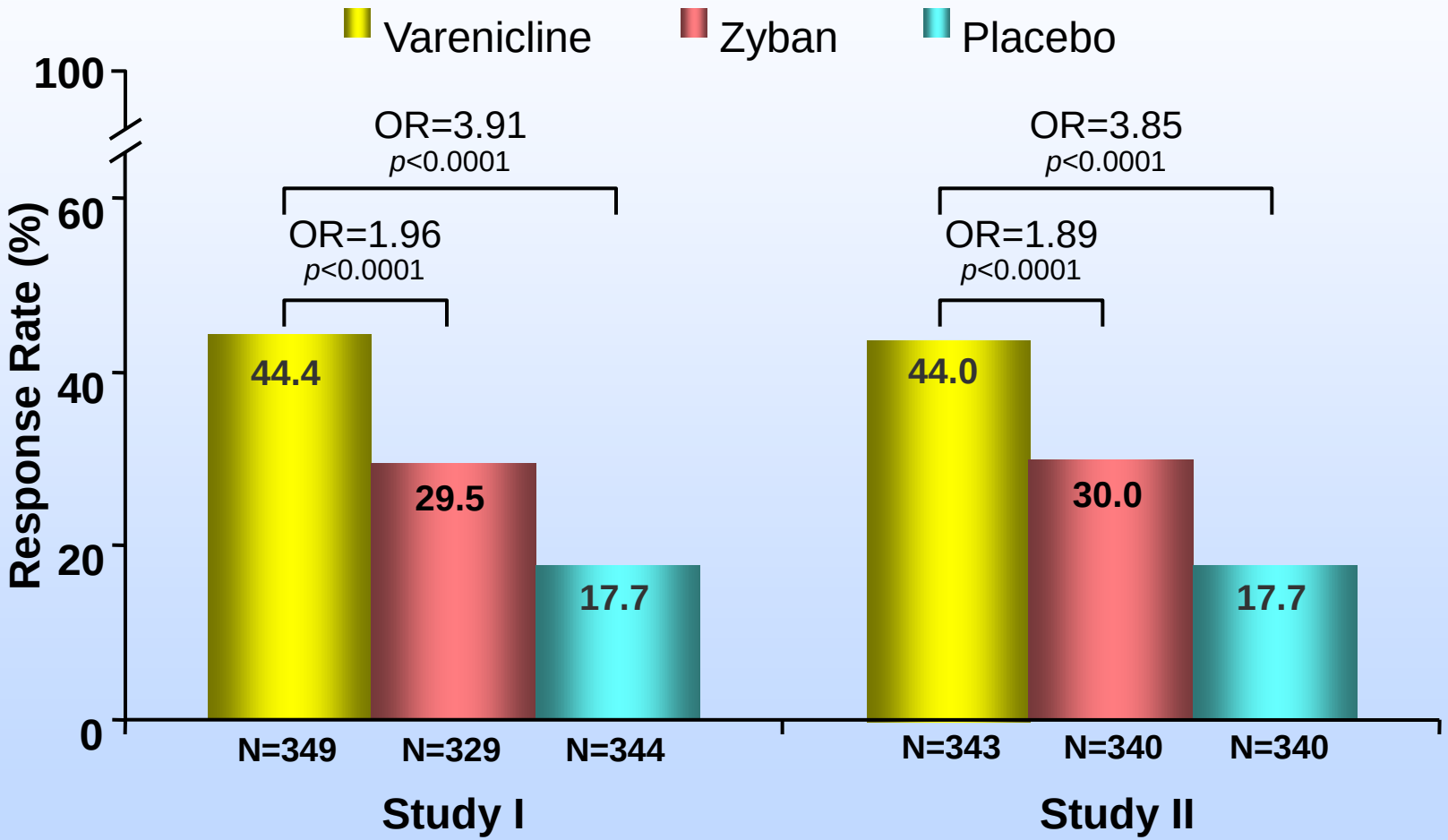
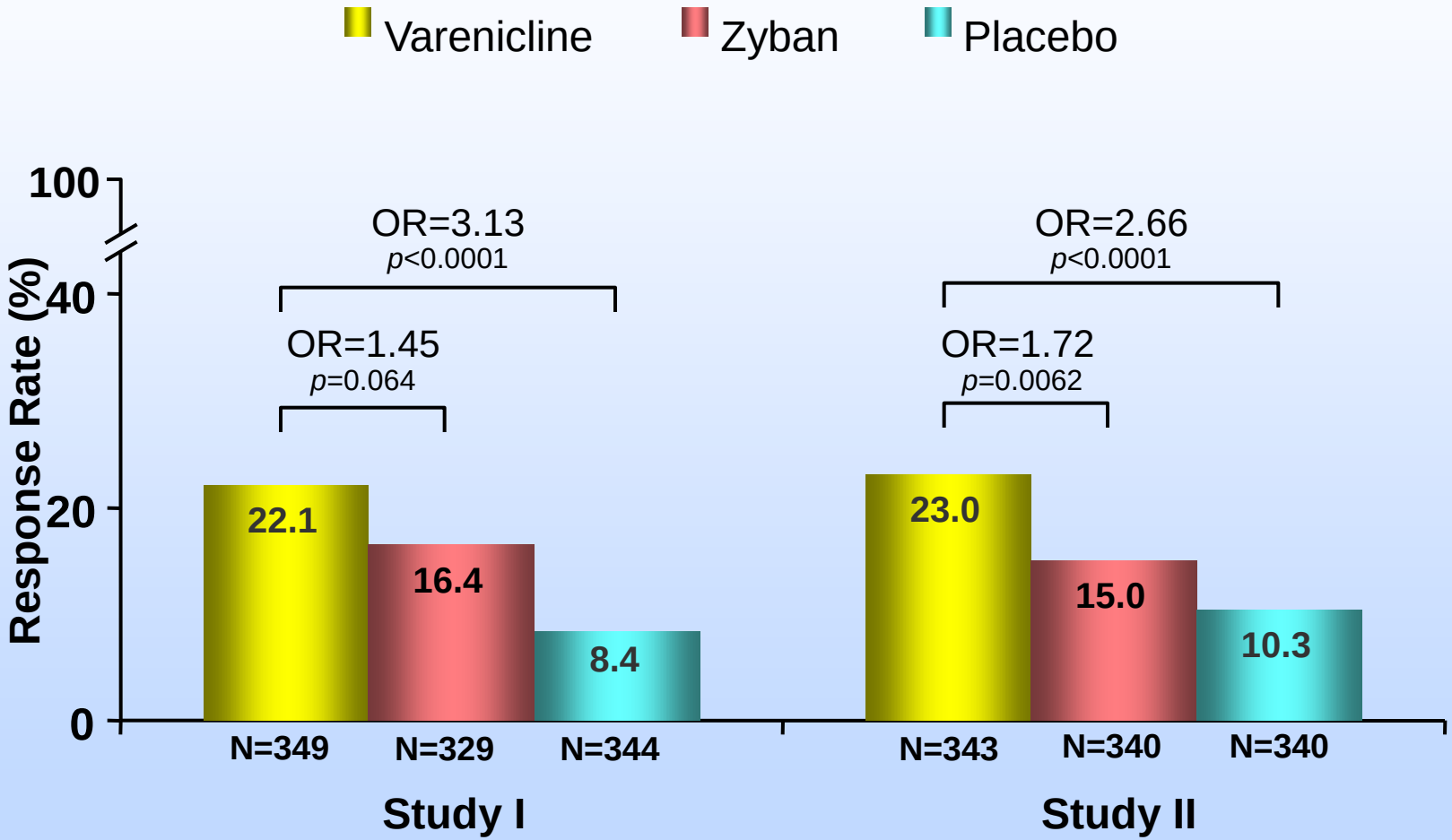
Pivotal Trails: CO-Confirmed Continuous Abstinence Rates Wks 9-12



Pivotal Trails: CO-Confirmed Continuous Abstinence Rates Wks 9-52



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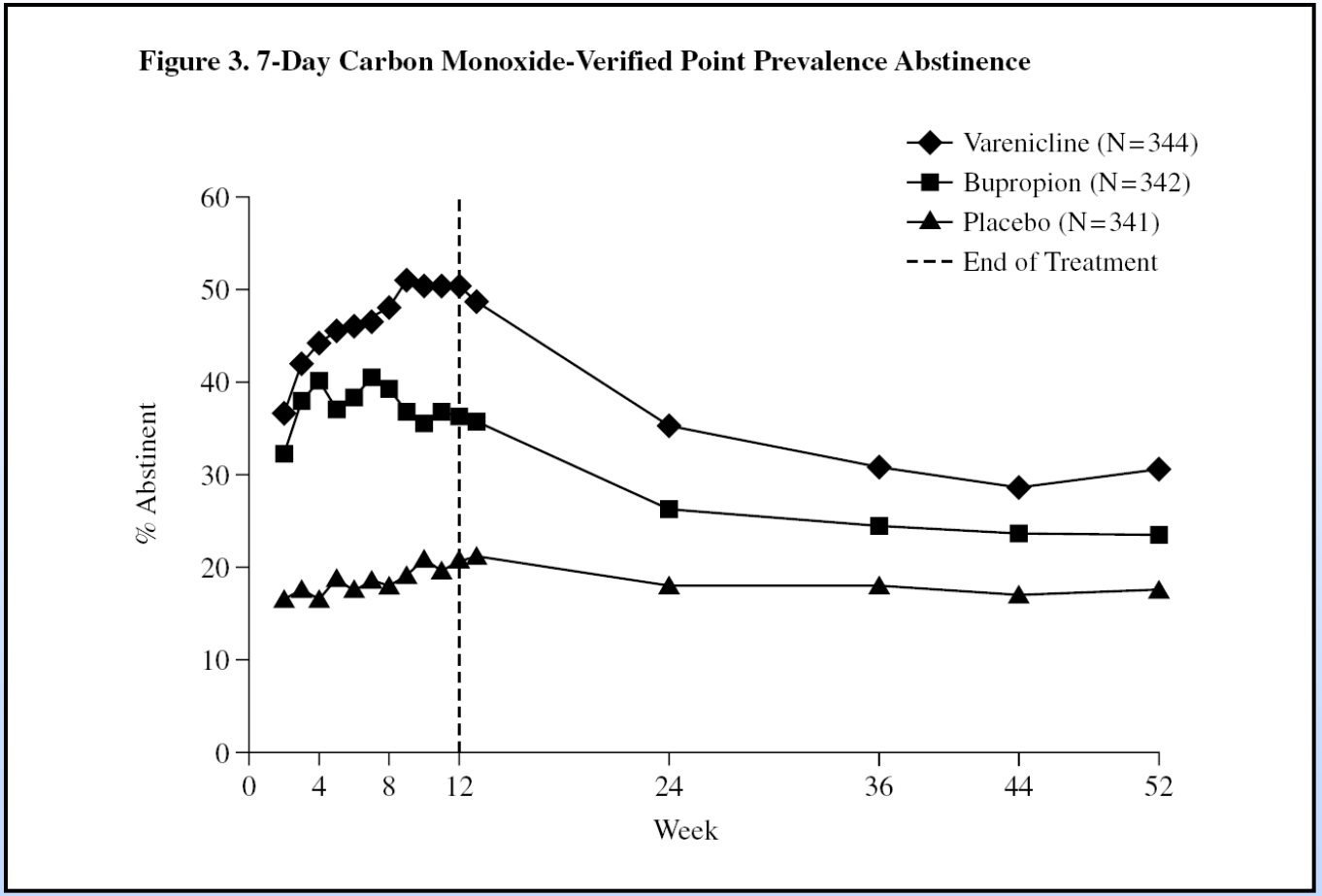
7-Day Point Prevalence Abstinence



Jorenby et al. JAMA 2006;296:56-63

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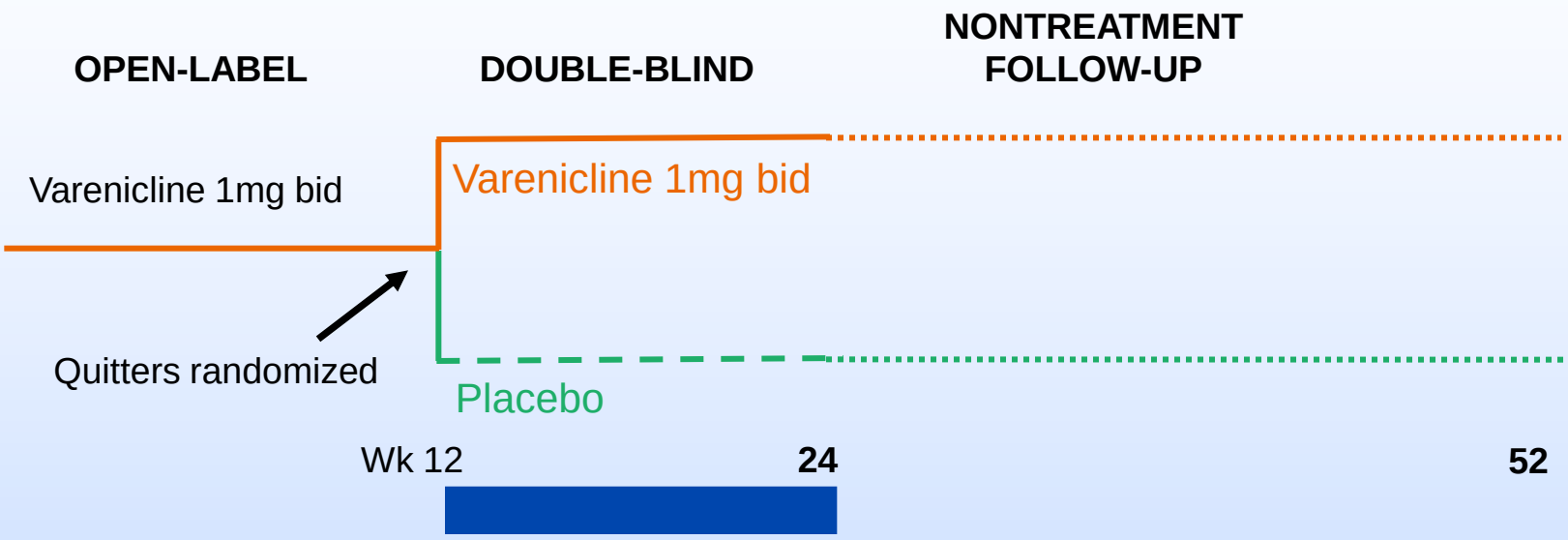
Maintenance of Abstinence: Study Design



Primary Endpoint:

- CO-confirmed continuous abstinence rate wk 13-24

Secondary Endpoint:

- CO-confirmed continuous abstinence rate wk 13–52

Tonstad et al. JAMA 2006;296:64-71

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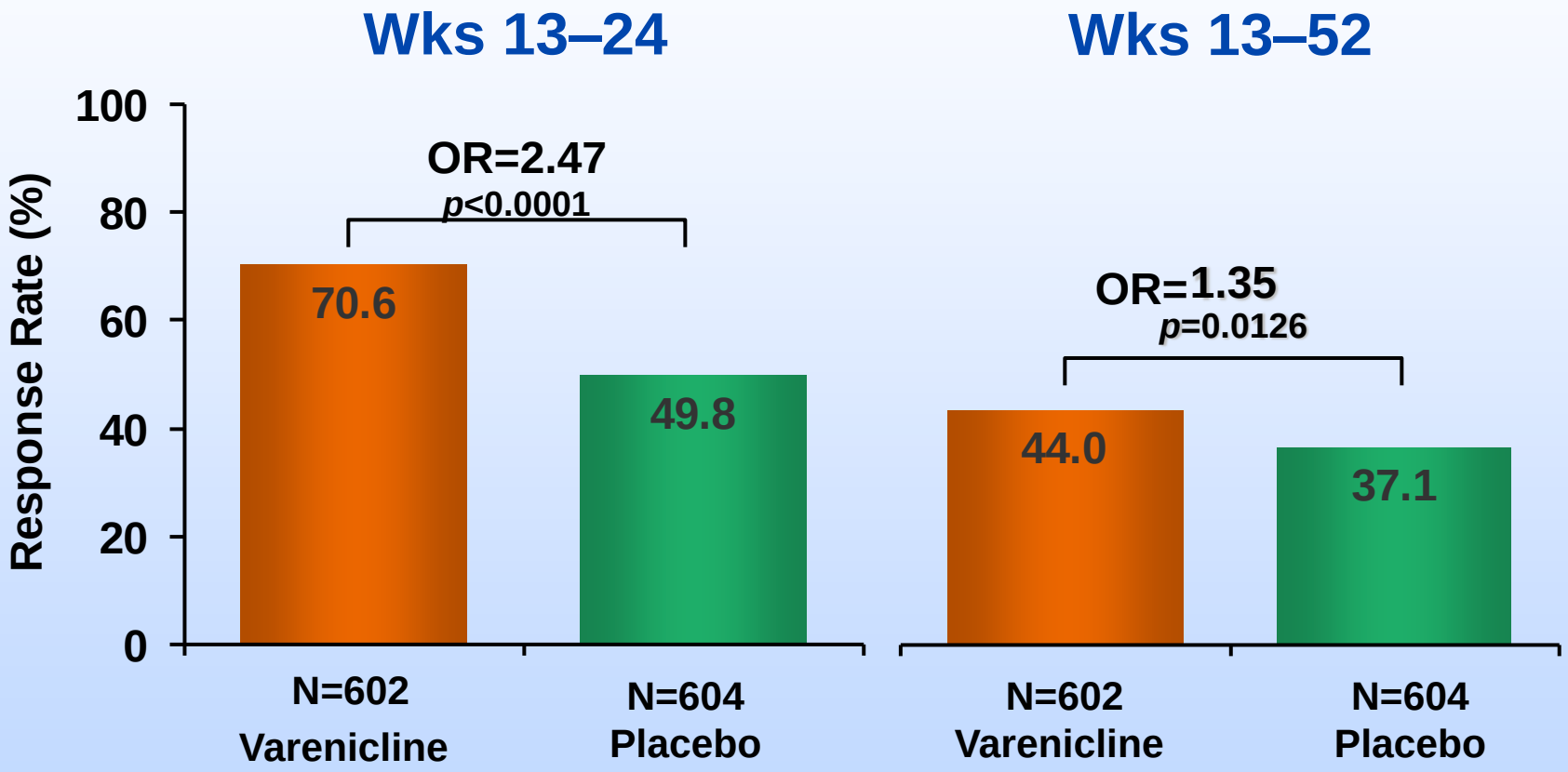
Maintenance of Abstinence Study: CO-confirmed Continuous Abstinence Rates



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Long Term Varenicline?

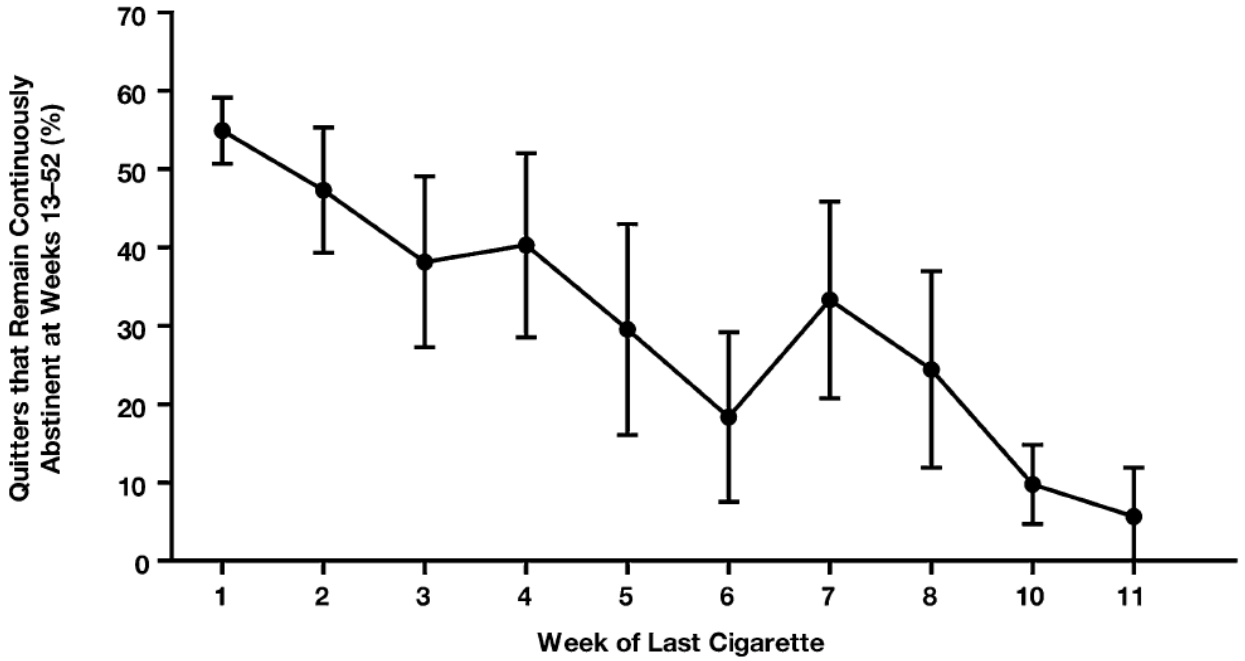

Figure 2 Proportions of patients abstinent at 1 year who had their last cigarette in weeks 1–11 (note: the figure combines the varenicline and placebo groups. The *ns* for each week of last cigarette are shown in Table 1; bars represent 95% confidence intervals for overall weeks 13–52 continuous abstinence rates)

Hajek et al. Addiction 2009; 104:1597-1602

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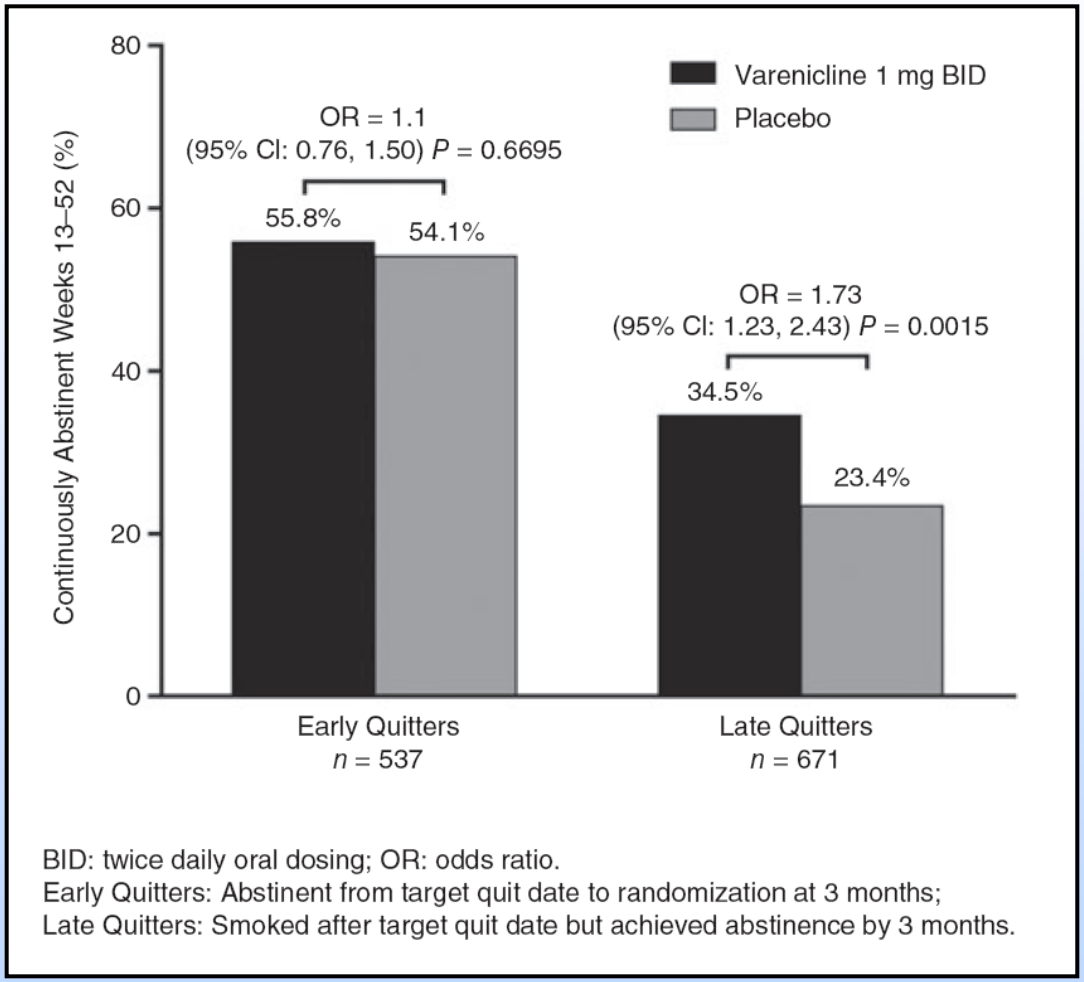
Effect of Long Term Varenicline



BID: twice daily oral dosing; OR: odds ratio.
Early Quitters: Abstinent from target quit date to randomization at 3 months;
Late Quitters: Smoked after target quit date but achieved abstinence by 3 months.

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Varenicline for Relapse Prevention

- Smokers who have risk factors for relapse
  - Heavier smokers
  - Other smokers in household
  - Comorbid mental health conditions
  - Past substance abuse
- Late quitters (smokers quitting well after their target quit date)

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Varenicline Prescribing and Safety

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Common Adverse Events in Clinical Trials (%)

	Varenicline	Placebo
Nausea	35.8	11.2
Insomnia	22	12.7
Abnl dreams	14.4	5
Headache	16.8	14.3
Other GI	22.5	11.8
Discontinued	12	8.1

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Varenicline: FDA Warning 2008

- All patients being treated with Chantix should be observed for neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior. These symptoms, as well as worsening of pre-existing psychiatric illness, have been reported in patients attempting to quit smoking while taking Chantix…

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CHANTIX®

(varenicline) Tablets

"Serious neuropsychiatric events, including, but not limited to depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking Chantix."

smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

"These events have occurred in patients with and without pre-existing psychiatric disease."

When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease

"Advise patients and caregivers that patients should stop taking Chantix and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior."

been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

(See **WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Post-Marketing Experience**)

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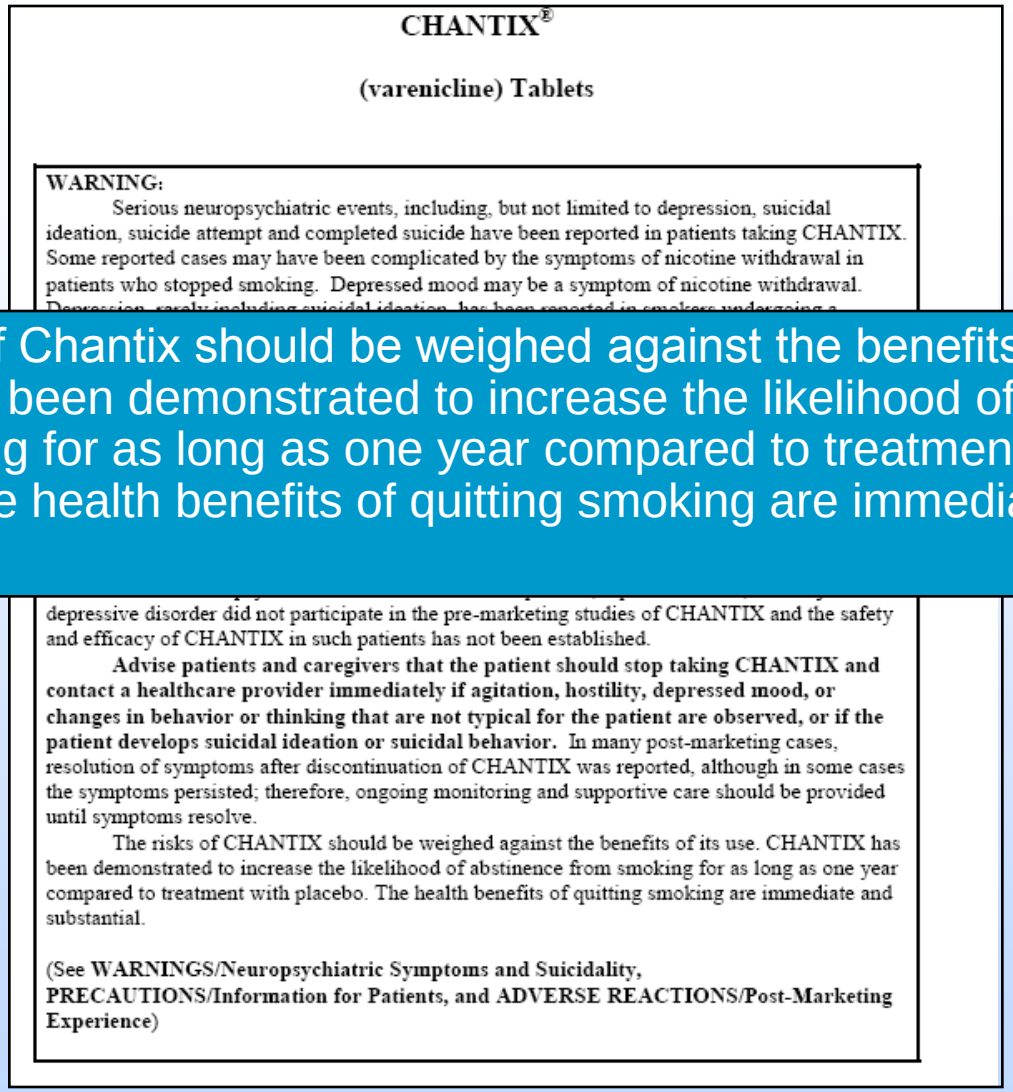

CHANTIX®

(varenicline) Tablets

WARNING:

Serious neuropsychiatric events, including, but not limited to depression, suicidal ideation, suicide attempt and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal.

"The risks of Chantix should be weighed against the benefits of its use. Chantix has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial."

depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

(See **WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Post-Marketing Experience**)

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Varenicline Boxed Warning

"The risk of serious adverse events while taking these products [Chantix and Zyban] must be weighed against the significant health benefits of quitting smoking. Smoking is the leading cause of preventable disease, disability, and death in the United States and we know these products are effective aids in helping people quit."

Janet Woodcock, M.D.
Director FDA Center for Drug Evaluation and Research
Press release, July 1, 2009

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Varenicline and Neuropsychiatric Symptoms

- Advise patients and family members that this has been observed
- Ask patients and/or family to report any symptoms like this to you
- Patients with serious psychiatric comorbidity were not included in clinical trials
- No cause and effect relationship has been established

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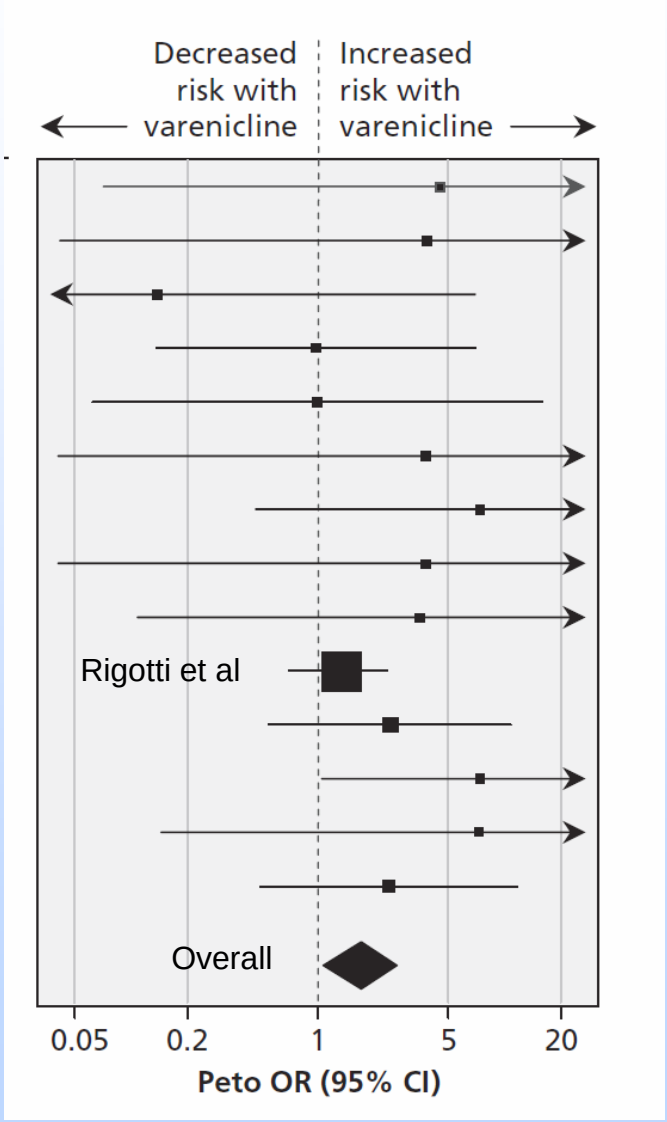
Varenicline and Cardiovascular Serious Adverse Events (SAE)



Overall CV SAE rates:

- Varenicline 52/4908 (1.06%)
- Placebo 27/3308 (0.82%)
- Peto OR 1.72 (95% CI 1.09 to 2.71)

Singh S, et al. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. CMAJ 2011 [July 4]. doi:10.1503/cmaj110218

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Varenicline and Cardiovascular Serious Adverse Events (SAE)

Hays JT. Varenicline for smoking cessation: is it a heartbreaker? CMAJ 2011 [July 4].doi:10.1503/cmaj110218

- *Problems with the Singh et al (CMAJ 2011) meta-analysis…*
  - Cardiovascular SAE's were rare in both groups
    - Only 0.82% placebo, and 1.06% varenicline
    - Absolute difference 0.24%
  - Greater numbers lost to follow-up in placebo arms
    - Lost opportunity to count CV events in placebo subjects
    - Bias in favor of fewer CV events ascertained in placebo arms
  - No adjudication of CV events in all but one study
  - The only clinical trial of varenicline efficacy among subjects with known CVD raised no safety concerns
    (Rigotti et al. Circulation 2010;121:221-229)

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Varenicline and cardiovascular risk

Hays JT. Varenicline for smoking cessation: is it a heartbreaker? CMAJ 2011 [July 4].doi:10.1503/cmaj110218

KEY POINTS

- When used as a treatment for tobacco dependence, varenicline may be associated with an increase in adverse cardiovascular events.
- The absolute increase in the rate of serious cardiovascular events associated with varenicline versus placebo is less than 1% based on analysis of more than 8200 participants involved in 13 randomized clinical trials.
- Smoking kills more than half of persistent smokers and reduces life expectancy by up to 10 years, whereas smoking cessation rapidly reduces the risk of future cardiovascular events.
- Varenicline should continue to be used with appropriate caution to limit adverse effects, while capitalizing on its benefits for smoking cessation.

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Additional Prescribing Information

- No dose reduction needed in…
  - Geriatric population
  - Patients with liver disease
- No important drug-drug interactions
- Reduce dose in renal impairment
  - Estimated creatinine clearance <30 ml/min reduce dose to 0.5 mg daily and titrate to 0.5 mg BID as tolerated

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Varenicline Prescribing

- Use in combination with behavioral treatment
- Start medication 1 week prior to target quit date
  - Days 1-3, Varenicline 0.5mg daily
  - Days 4-7, Varenicline 0.5mg twice daily
  - Day 8 to end of treatment 1.0mg twice daily
  - TQD on day 8
- Take with food
- Dose reduction with severe renal impairment
- Supplied as starter card (11X0.5mg tabs) and 4-week packs of 1 mg BID or bottles of 56
- Treat for 3 to 6 months

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Nicotine Vaccine

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Nicotine Vaccine

- Nicotine alone does not generate an immune response when injected
- When nicotine is attached to a large molecule (conjugated) it does cause an immune response
- Early trials with conjugate nicotine vaccine indicate an immune response in most smokers

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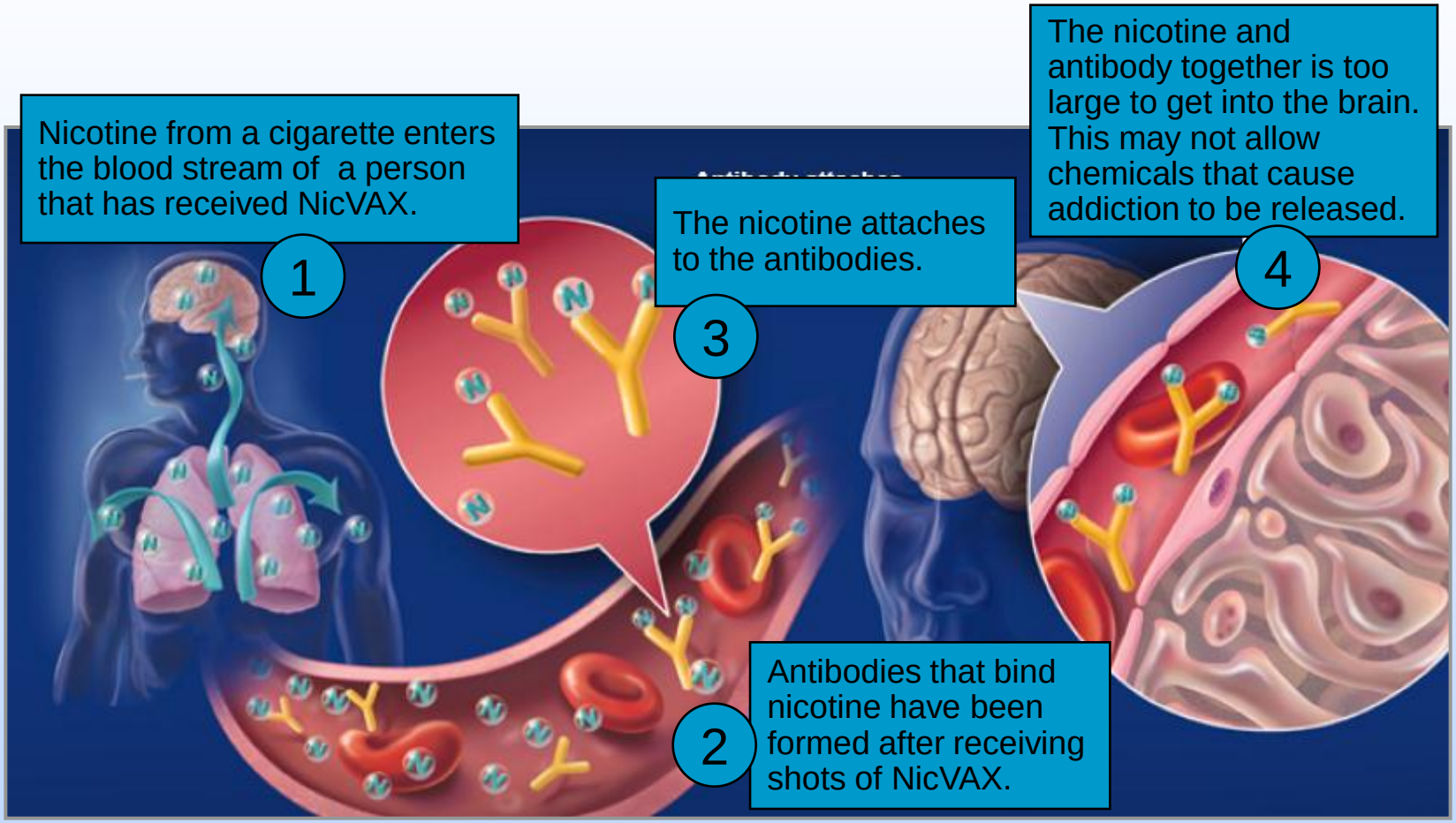
How Does NicVAX Work?



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Nicotine Vaccine

- Nicotine vaccine is provided through a series of injections (4-6) over 3-4 months
- Antibodies to nicotine build over this time
- Nicotine from cigarettes is bound by antibodies causing…
  - Sequestration of nicotine in the blood
  - Inability of nicotine to enter the brain
- Reduced + reinforcement from smoking
- Preliminary evidence from Phase III study shows no benefit for smoking abstinence

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GABA and Glutamate
Novel Neurotransmitter Targets

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Gabapentin: Open-Label Pilot Trial Results Abstinence Outcomes

Characteristic	% Abstinent	95% C.I.
End of treatment		
7-day point prevalence	28	16 to 42
Prolonged abstinence	24	13 to 38
6-months		
7-day point prevalence	20	10 to 34
Prolonged abstinence	16	7 to 29

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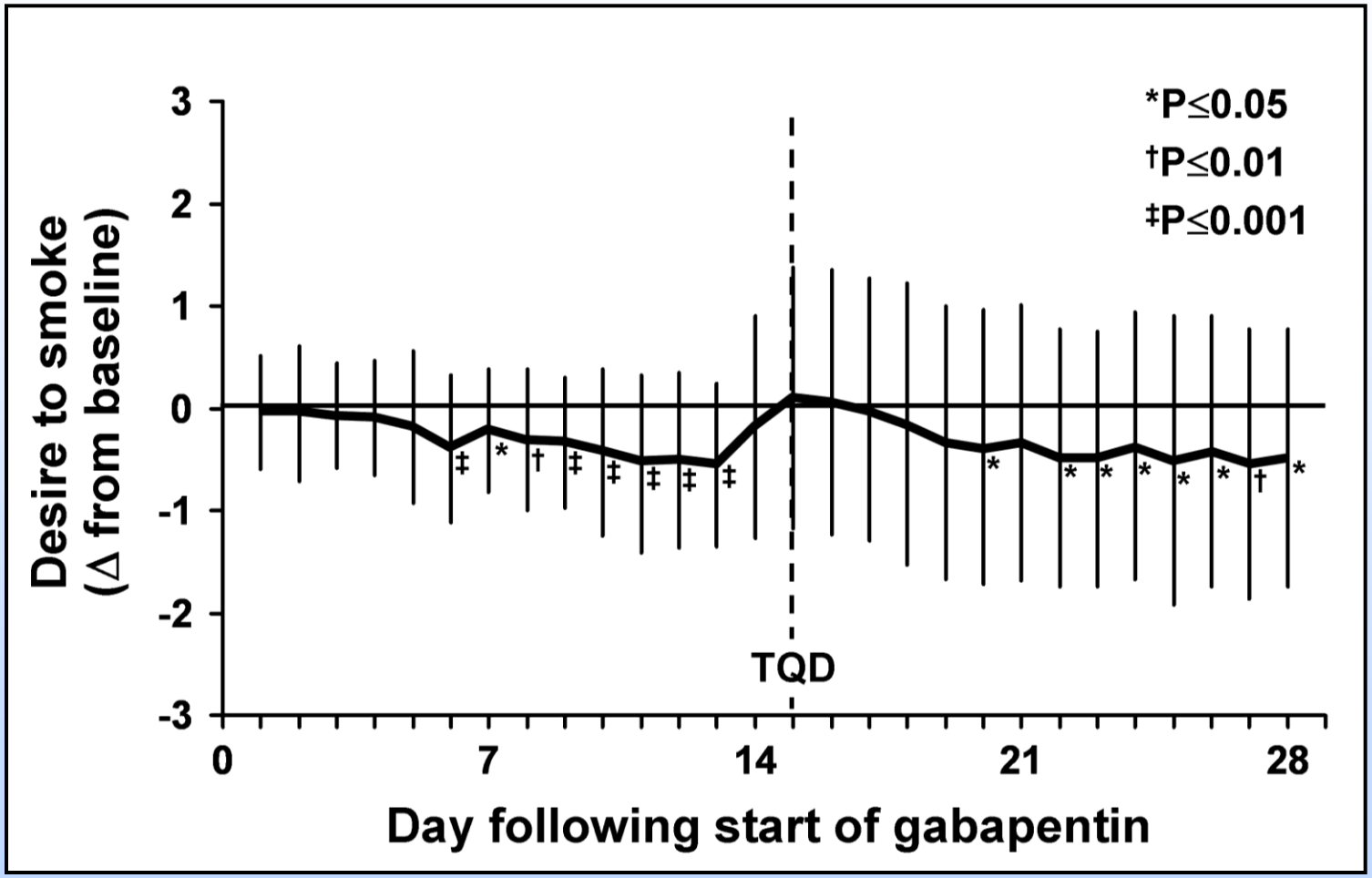
Gabapentin: Reduced the Desire to Smoke



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Drugs Targeting GABA and Glutamate

- Glutamatergic agents
  - Dextromathorphan
  - Topiramate
- GABA-ergic agents
  - Baclofen
  - Tiagibine
  - Acamprosate
  - Topiramate

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Endocannabinoids

Rimonabant: An EC-1 Receptor Blocker

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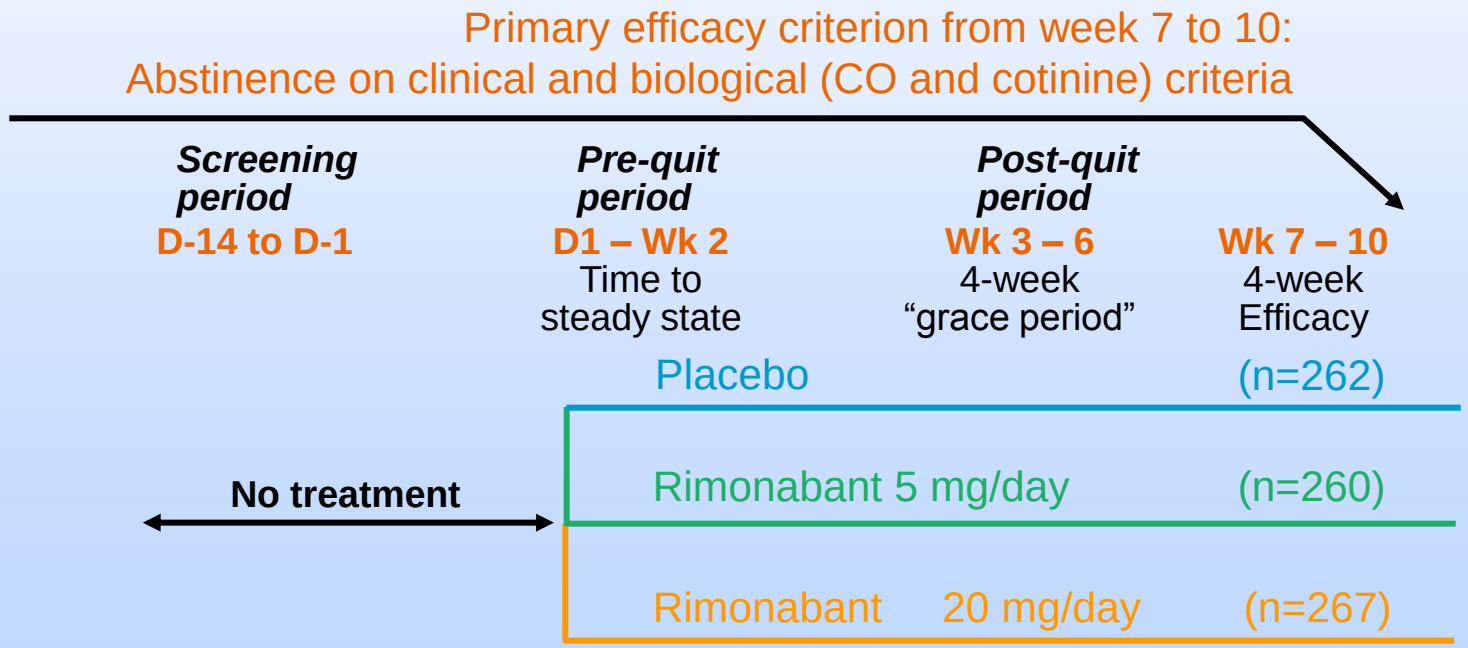
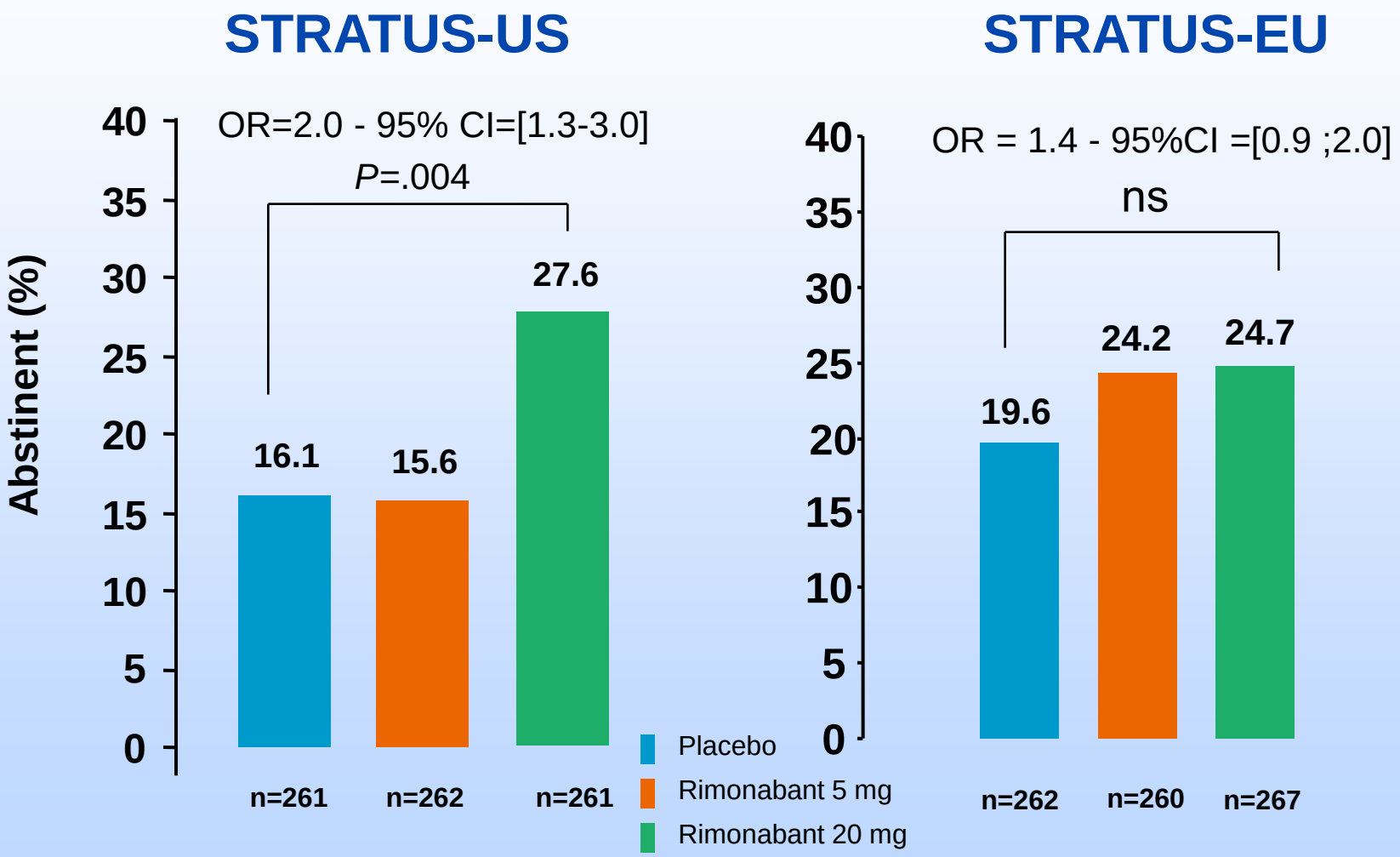
STRATUS-US / STRATUS-EU

- Design:
  - Multiple-country, multicenter, double-blind, 3-arm, placebo-controlled, randomized, parallel-group, fixed-dose, 10-week active treatment (42-week follow-up), phase III trial



End of Treatment 4-Week Abstinence



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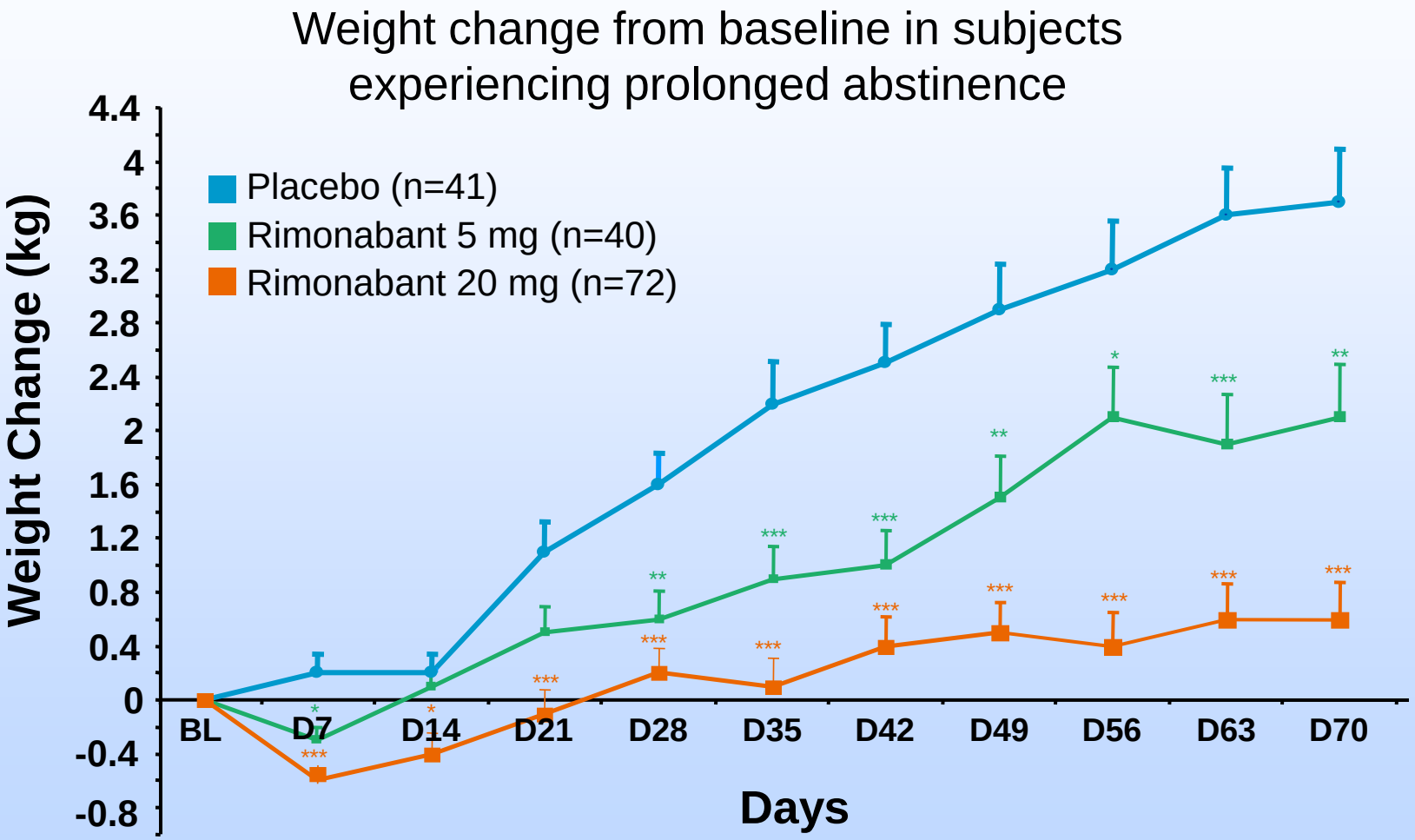
Weight Change: 4-Week Continuous Abstinence



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Rimonabant: Adverse Effects

- Side Effects ≥10% Nausea
  - Headaches
  - Upper Respiratory Infections
  - Diarrhea
  - Insomnia
- Neuropsychiatric symptoms

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Pharmacologic Treatment of Tobacco Dependence

- Varenicline a partial nAChR agonist
  - Effective compared to placebo and bupropion
  - Safety concerns have arisen
- Nicotine Vaccine immunotherapy- promising?
- New therapeutic targets to exploit
  - GABA-ergic and glutamatergic agents
  - Endocannabinoid receptor blockers
  - Endogenous opioid antagonists

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Summary

- Varenicline is efficacious for the treatment of tobacco dependence
- Side effects have been generally mild and well-tolerated
- Varenicline is as effective as other first-line treatments for tobacco dependence
- Monitor patients for new neuropsychiatric symptoms while on therapy

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