Pharmacotherapy for Tobacco Dependence Treatment

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UpToDate: royalties

OVERVIEW

- Which medications are effective?
- Newer evidence
  - Cytisine
  - New ways to make old drugs more effective
  - Safety of varenicline

PHARMACOTHERAPY

1st Line - 2008 US Public Health Service Guidelines

- Nicotine replacement
  - Skin patch
  - Gum
  - Lozenge
  - Oral inhaler
  - Nasal spray
- Bupropion SR *(Zyban,Wellbutrin)*
- Varenicline *(Chantix/Champix)*

Each ~doubles the odds of quitting vs. placebo

OTHER DRUGS

- With evidence of efficacy
  - Nortriptyline
  - Clonidine
  - Cytisine

CYTISINE

- Similar mechanism of action as varenicline
- Unusual dosing schedule
- Differs from varenicline in pharmacokinetics and cost

Table 1: Cytisine compared to varenicline

	Half life	Treatment period	Cost for full course (US$)[4]
Cytisine	4.8 hours[5]	Titrated down over 25 days	$15-$20
Varenicline	17 hours[6]	Titrated up over 12 weeks	$474-501

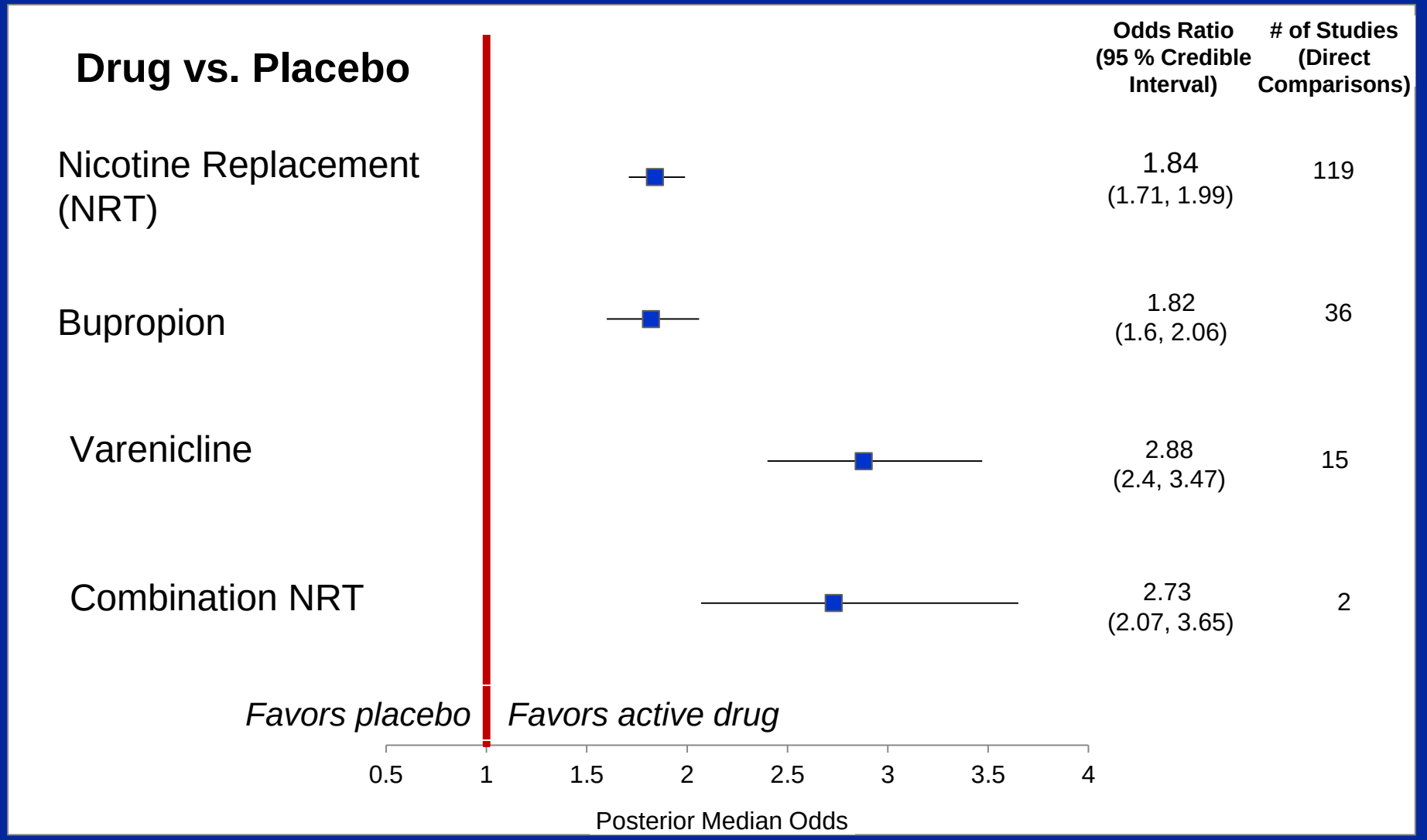
CYTISINE

A Cost-Effective Tobacco Treatment Hiding in Plain Sight

- Superior to placebo in 5 trials (OR 3.3, 95% CI 1.9-5.9)
- Comparable to nicotine patch in 1 trial (low quit rates)
- Well tolerated
- Available in 17 countries (Central & Eastern Europe)
- But not licensed in the rest of the world
- Challenge: how to get regulatory approval in US/EU, which will make open the door to global availability?

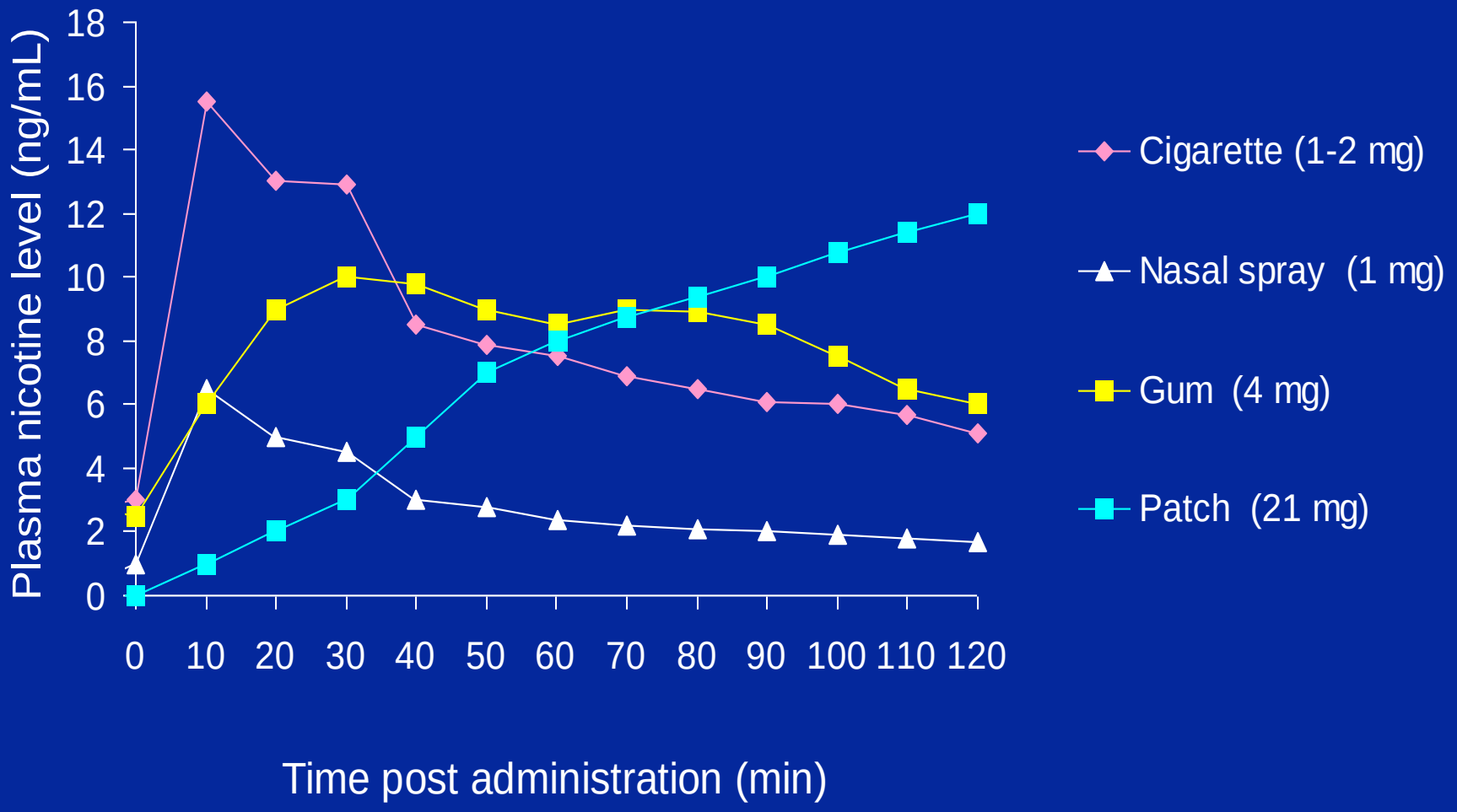
Current Pharmacotherapy Options

Cochrane meta-analysis, 2013 (JAMA. 2014;311:193-194)



PLASMA NICOTINE LEVELS

Cigarettes vs. Nicotine Replacement Products



NICOTINE REPLACEMENT

Long-acting, slow onset → *skin patch*

- Constant nicotine level to avoid withdrawal
- Simplest to use, best compliance
- User has no control of dose

Short-acting, faster onset

→ ***oral*** *(gum, lozenge, inhaler)*

→ ***nasal*** *(spray)*

- User controls dose
- Nicotine blood levels fluctuate more
- Requires more training to use properly

Newer Ways to Use Old Drugs

- Combine short- and long-acting NRT
- Treat longer to prevent relapse
- Start NRT *before* quit day
- Use varenicline or NRT in those not ready to quit now
  - "Reduce to quit" (gradual reduction)

Current Pharmacotherapy Options

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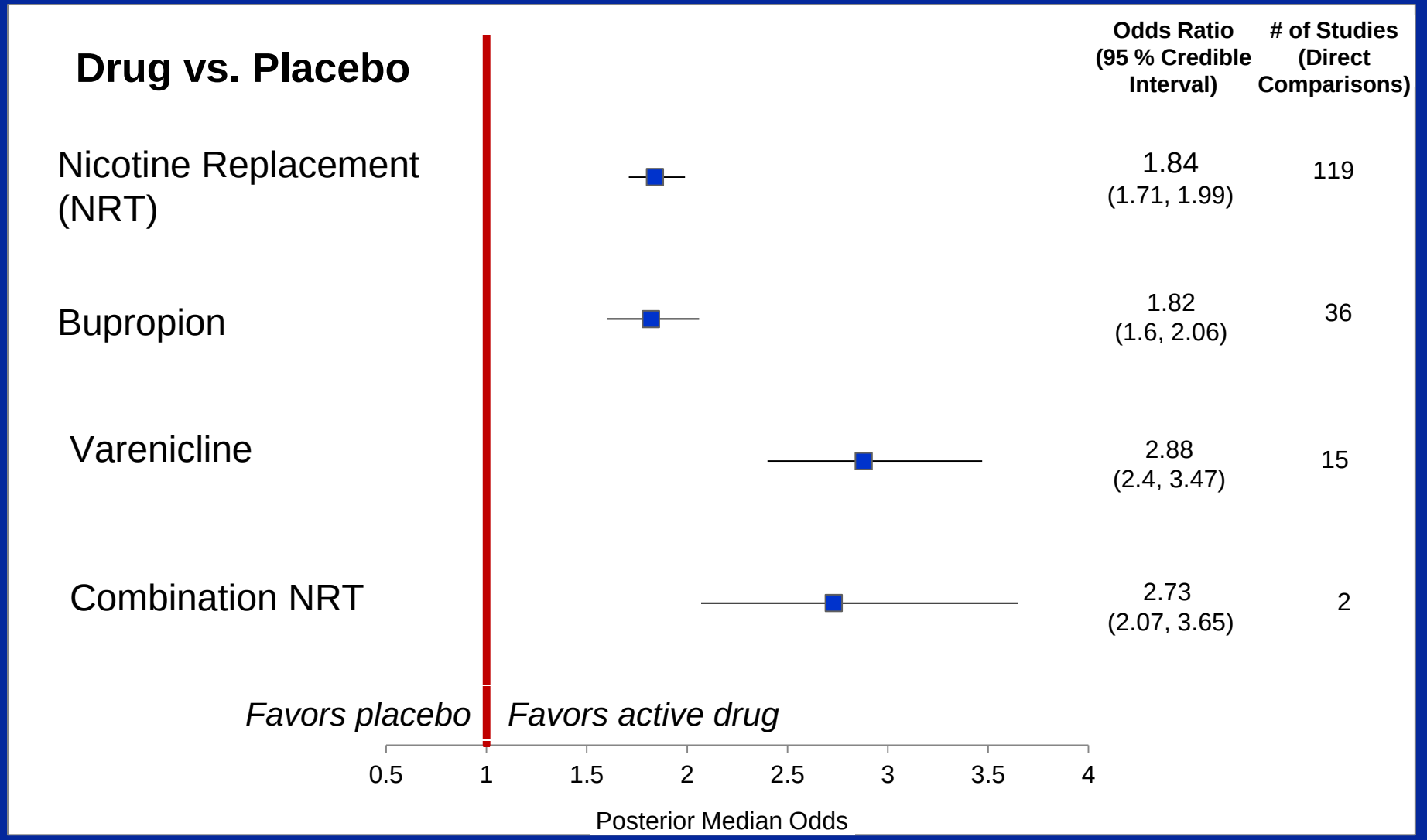


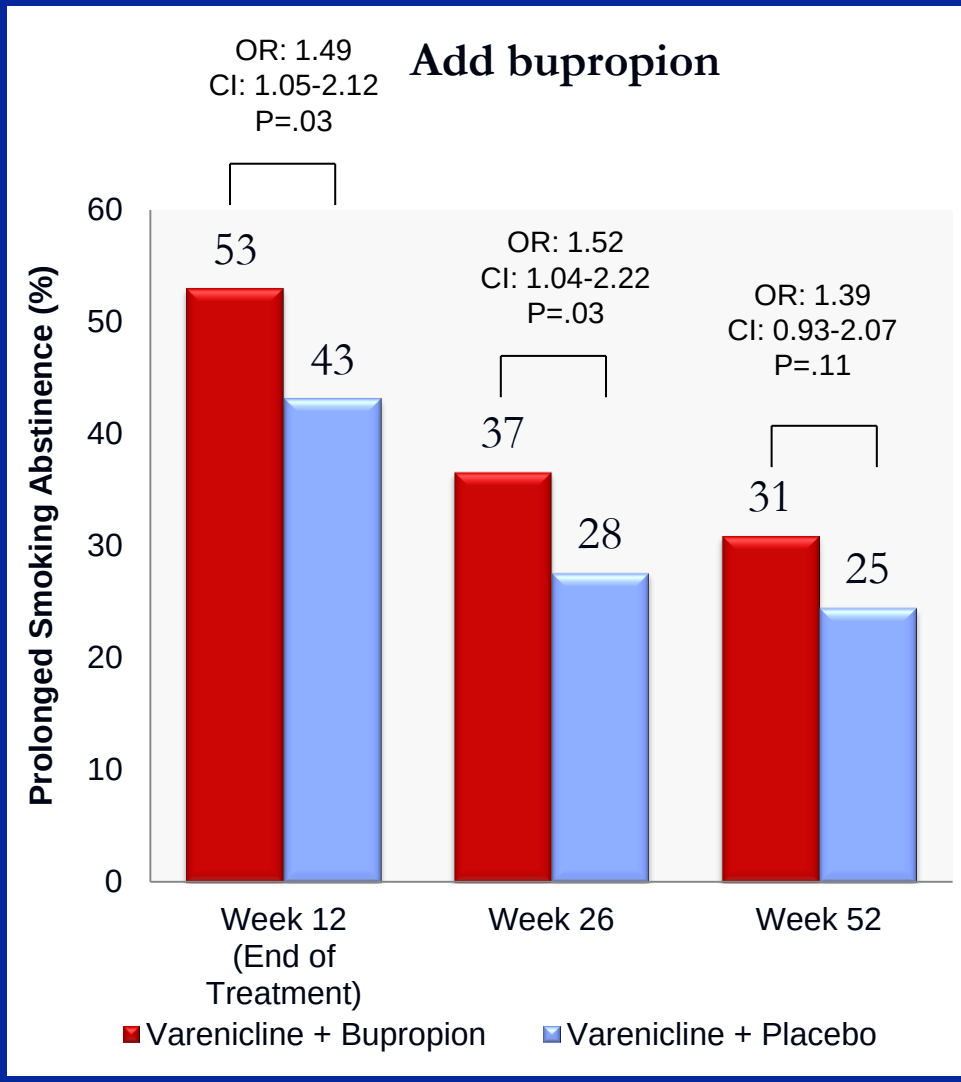
Combining Drugs Across Classes

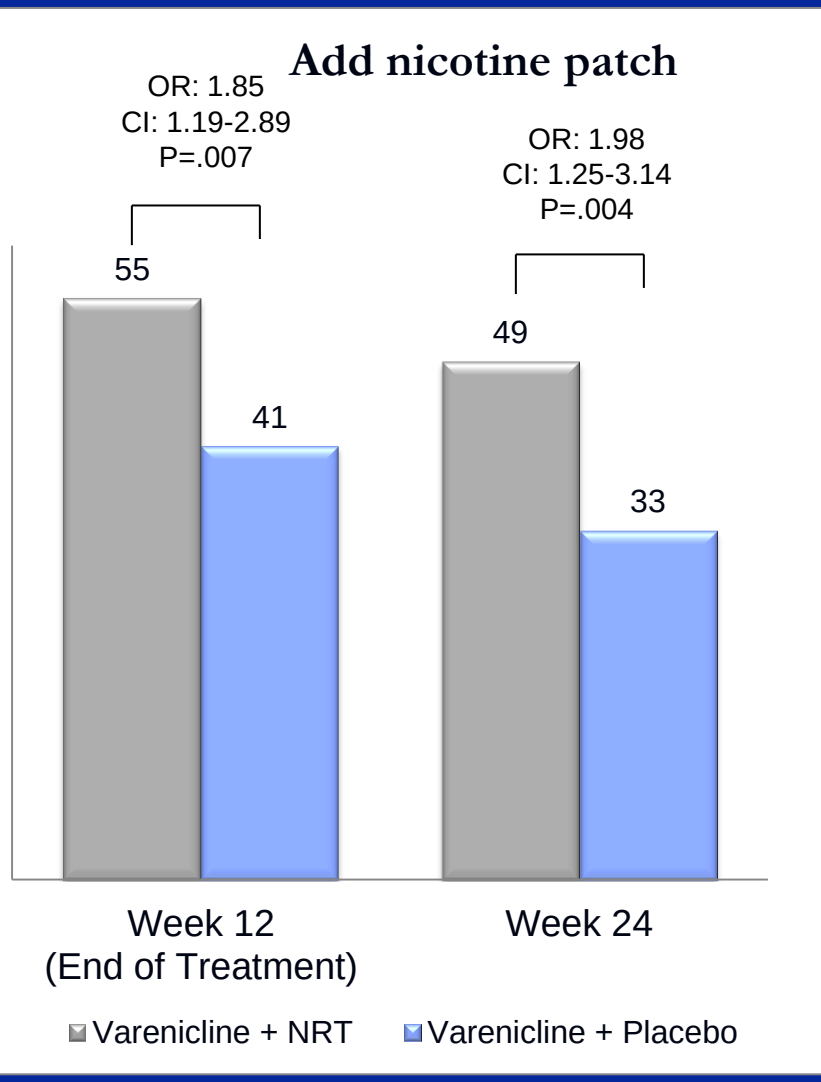
Is there a Tier 3?

- Does combining drugs of different classes improve quit rates?

- 2 placebo controlled randomized trials were published in 2014
  - Each started with varenicline
  - 1 added bupropion (vs. placebo)
  - 1 added nicotine patch (vs. placebo)

Adding Bupropion or NRT to Varenicline





Ebbert JO. JAMA. 2014;311:193-194.

Koegelenberg C. JAMA 2014; 312:155.

Results of a New Randomized Trial

Baker et al. JAMA 2016

N=1086

- Head-to-head, open label RCT compared
  - Nicotine patch
  - Nicotine patch + lozenge
  - Varenicline
- Surprising result
  - No difference in CO-confirmed quit rates at 6 or 12 months

VARENICLINE SAFETY

FDA Public Health Advisory, *July 2009*

- "[Varenicline] or [bupropion] has been associated with reports of changes in behavior such as hostility, agitation, depressed mood, and suicidal thoughts or actions."

- "FDA is requiring the manufacturers of both products to add a new ***Boxed Warning***

VARENICLINE SAFETY

The dilemma

- Stopping smoking produces nicotine withdrawal symptoms *(depressed mood, anxiety, and irritability)*
- When these symptoms occur in a smoker who is stopping smoking on varenicline, did the drug or did quitting smoking cause the symptom?
- Case reports cannot answer this question
- Double-blind RCTs could. A 2015 meta-analysis of 39 varenicline RCTs → no excess of depression or suicidal thoughts (but few patients had mental illnes).*

*Thomas KH, BMJ 2015;350:h1109

EAGLE Randomized Trial

Nicotine patch vs. bupropion vs. varenicline vs. placebo

8000 smokers (4000 with + 4000 without psychiatric diagnosis)

Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial

Robert M Anthenelli, Neal L Benowitz, Robert West, Lisa St Aubin, Thomas McRae, David Lawrence, John Ascher, Cristina Russ, Alok Krishen, A Eden Evins

Summary

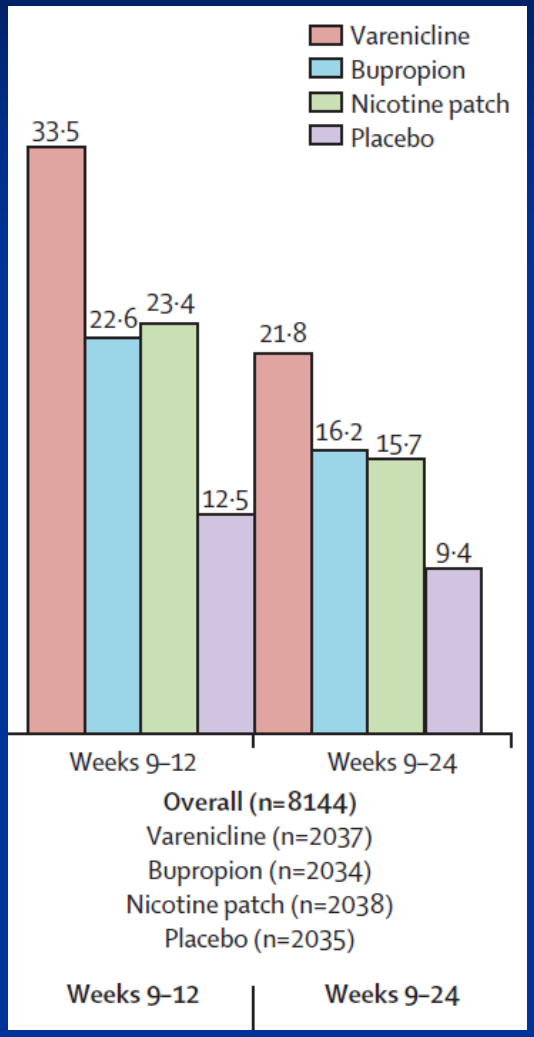
Background Substantial concerns have been raised about the neuropsychiatric safety of the smoking cessation medications varenicline and bupropion. Their efficacy relative to nicotine patch largely relies on indirect comparisons, and there is limited information on safety and efficacy in smokers with psychiatric disorders. We compared the relative neuropsychiatric safety risk and efficacy of varenicline and bupropion with nicotine patch and placebo in smokers with and without psychiatric disorders.

Methods We did a randomised, double-blind, triple-dummy, placebo-controlled and active-controlled (nicotine patch; 21 mg per day with taper) trial of varenicline (1 mg twice a day) and bupropion (150 mg twice a day) for 12 weeks with 12-week non-treatment follow-up done at 140 centres (clinical trial centres, academic centres, and outpatient clinics) in 16 countries between Nov 30, 2011, and Jan 13, 2015. Participants were motivated-to-quit smokers with and without psychiatric disorders who received brief cessation counselling at each visit. Randomisation was computer generated (1:1:1:1 ratio). Participants, investigators, and research personnel were masked to treatment assignments. The primary endpoint was the incidence of a composite measure of moderate and severe neuropsychiatric adverse events. The main efficacy endpoint was biochemically confirmed continuous abstinence for weeks 9–12. All participants randomly assigned were included in the efficacy analysis and those who received treatment were included in the safety analysis. The trial is registered at ClinicalTrials.gov (number NCT01456936) and is now closed.

Lancet 2016

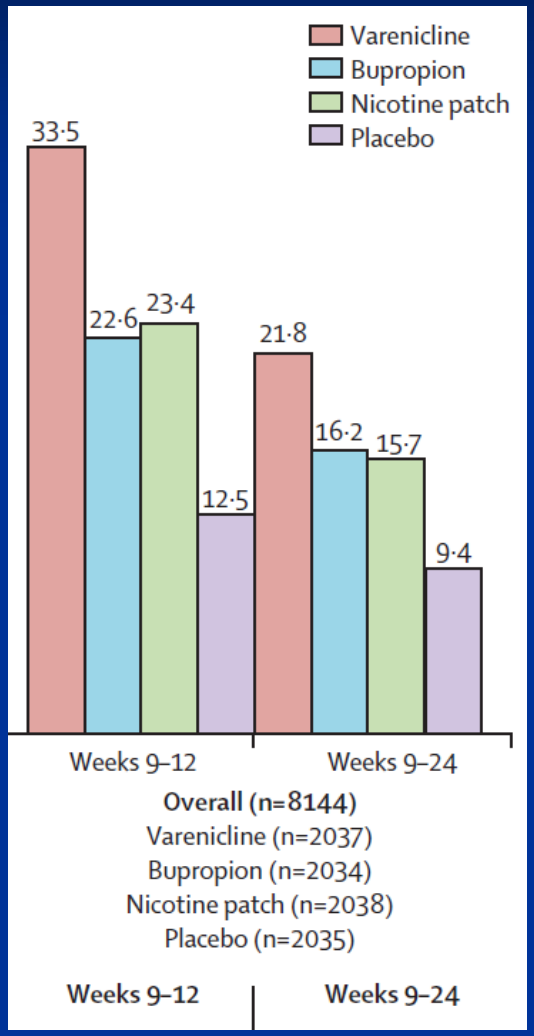
EAGLE: Efficacy and Safety Outcomes

Continuous abstinence
(Efficacy)



EAGLE: Efficacy and Safety Outcomes

Continuous abstinence (Efficacy)



Composite neuropsychiatric event endpoint (Safety)

	Non-psychiatric cohort* (n=3984)			
	Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)
Primary composite neuropsychiatric endpoint	13 (1·3%)	22 (2·2%)	25 (2·5%)	24 (2·4%)
Estimated primary composite neuropsychiatric adverse events (% [95% CI])	1·25% (0·60 to 1·90)	2·44% (1·52 to 3·36)	2·31% (1·37 to 3·25)	2·52% (1·58 to 3·46)
Difference in risk of composite primary endpoint (RD% [95% CI])				
Versus placebo	−1·28 (−2·40 to −0·15)	−0·08 (−1·37 to 1·21)	−0·21 (−1·54 to 1·12)	..
Versus nicotine patch	−1·07 (−2·21 to 0·08)	0·13 (−1·19 to 1·45)	..	..
Versus bupropion	−1·19 (−2·30 to −0·09)	..	..	..

	Psychiatric cohort* (n=4074)			
	Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
Primary composite neuropsychiatric endpoint	67 (6·5%)	68 (6·7%)	53 (5·2%)†	50 (4·9%)
Estimated primary composite neuropsychiatric adverse events (% [95% CI])	6·42% (4·91 to 7·93)	6·62% (5·09 to 8·15)	5·20% (3·84 to 6·56)	4·83% (3·51 to 6·16)
Difference in risk of composite primary endpoint (RD% [95% CI])				
Versus placebo	1·59 (−0·42 to 3·59)	1·78 (−0·24 to 3·81)	0·37 (−1·53 to 2·26)	..
Versus nicotine patch	1·22 (−0·81 to 3·25)	1·42 (−0·63 to 3·46)	..	..
Versus bupropion	−0·20 (−2·34 to 1·95)	..	..	..

VARENICLINE SAFETY

My Bottom Line

- Prescribing any drug requires balancing risks and benefits.
  - Continuing to smoke is clearly hazardous
  - Varenicline is one of the most effective drugs available to treat tobacco dependence
  - Varenicline can cause psychiatric symptoms in some
  - Sum of evidence does not suggest that it is more hazardous than other cessation meds, even in patients with comorbid psychiatric illness.
  - Patients given varenicline should be followed

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SUMMARY

- We have effective medications to help smokers quit, but they are not perfect.
- We could get more benefit from existing medications if
  - We identified optimal use of medications we have
    - Combining medications (stepped care approaches)
    - Harm reduction or reduce to quit paradigms
  - More smokers used them
    - Make them affordable
    - Make their use routine in health care systems
- Cytisine is a promising drug that could make a difference if it was both available and affordable.

Message to Hospitals and Clinics

Treat Tobacco Use Like a Chronic Disease

It needs long-term management and as much of your attention as treating hypertension and diabetes