

Combination of varenicline and nicotine replacement therapy: a real therapeutic option in smoking cessation?

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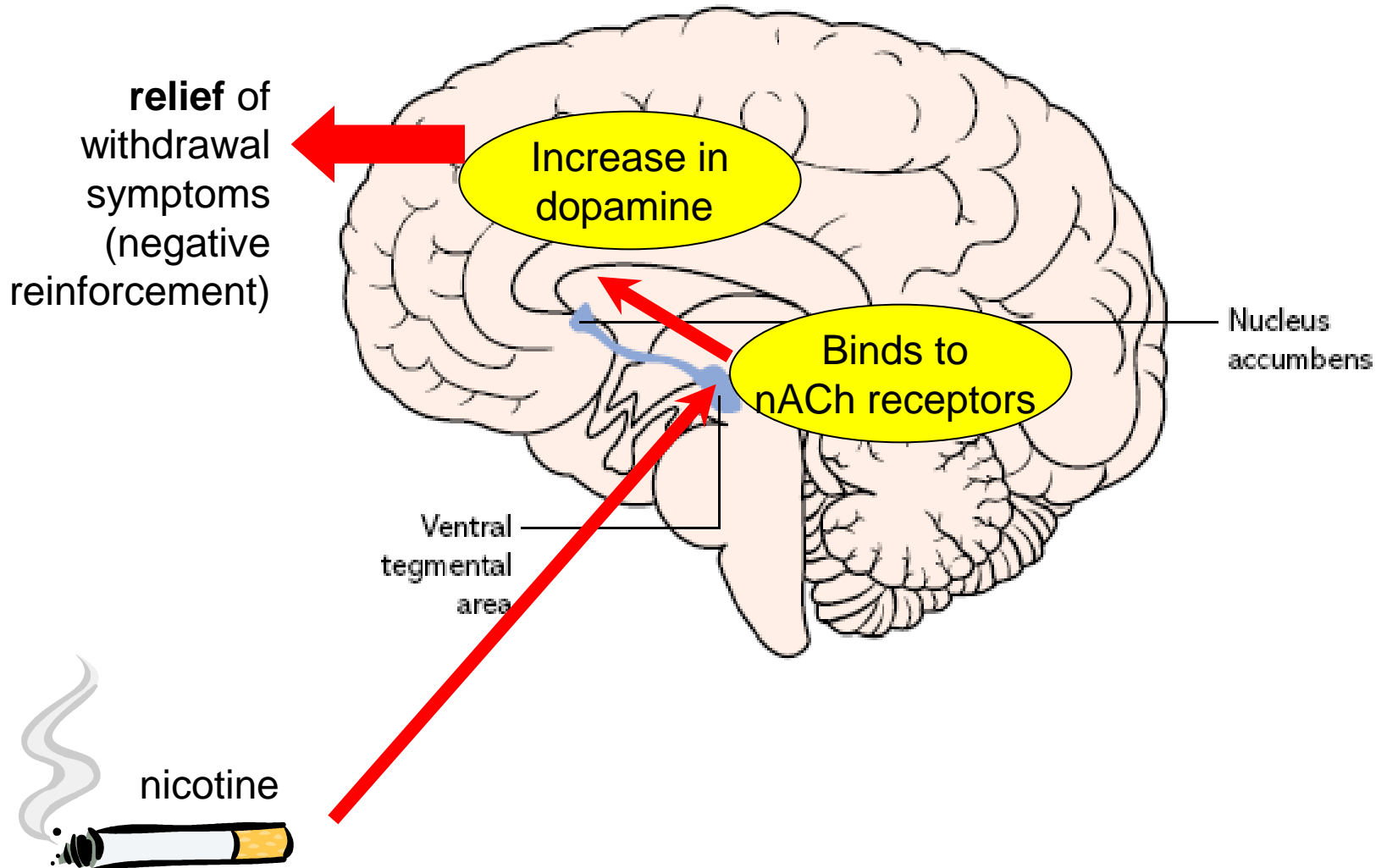
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Tobacco Dependence

- A recognised disorder (DSM-IV)
- Requires treatment
- It is estimated that around half of all smokers will not be able to stop without some form of help

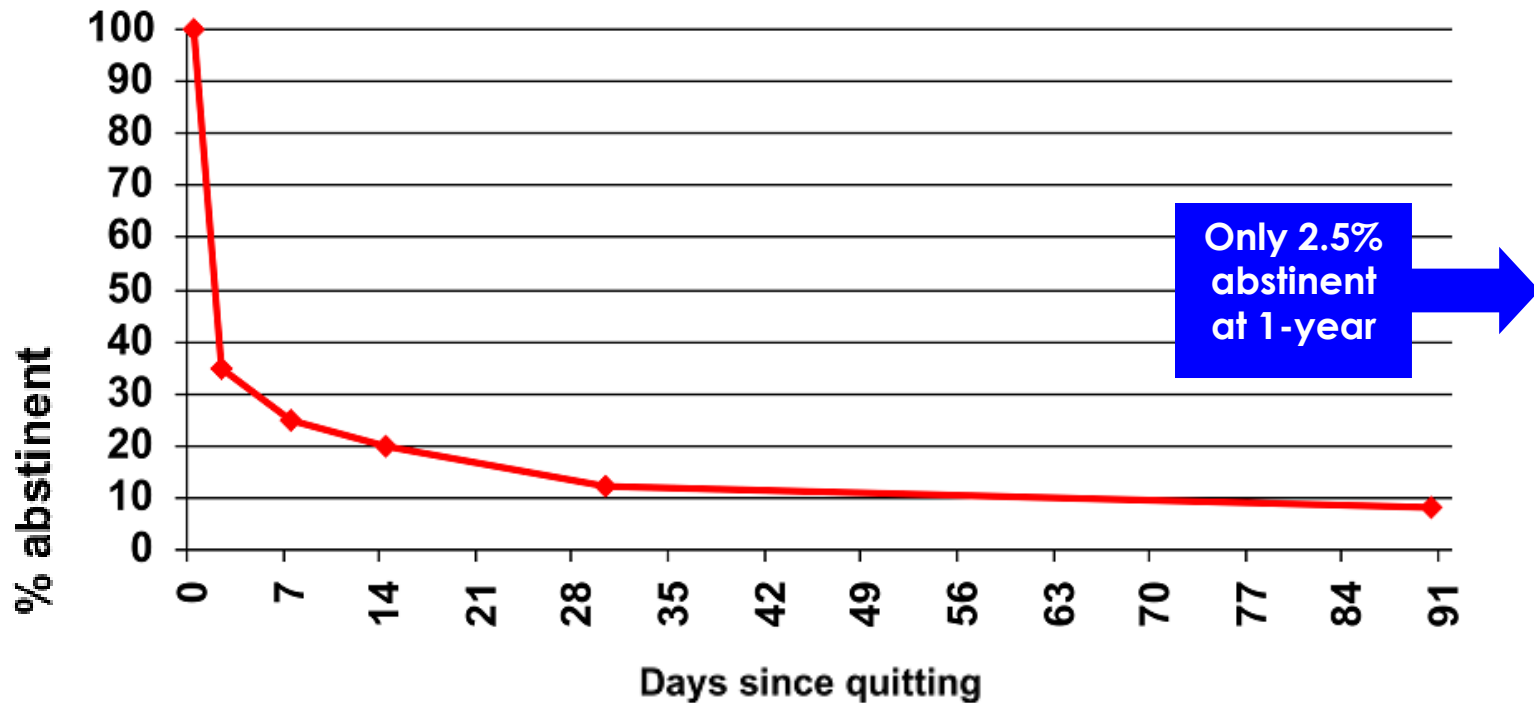


Mesolimbic dopamine pathway



Quitting without support

- The majority of people who quit without support will relapse in the first week



Hughes et al. (2004) Shape of the relapse curve and long-term abstinence among untreated smokers, *Addiction*, 99 29–38.



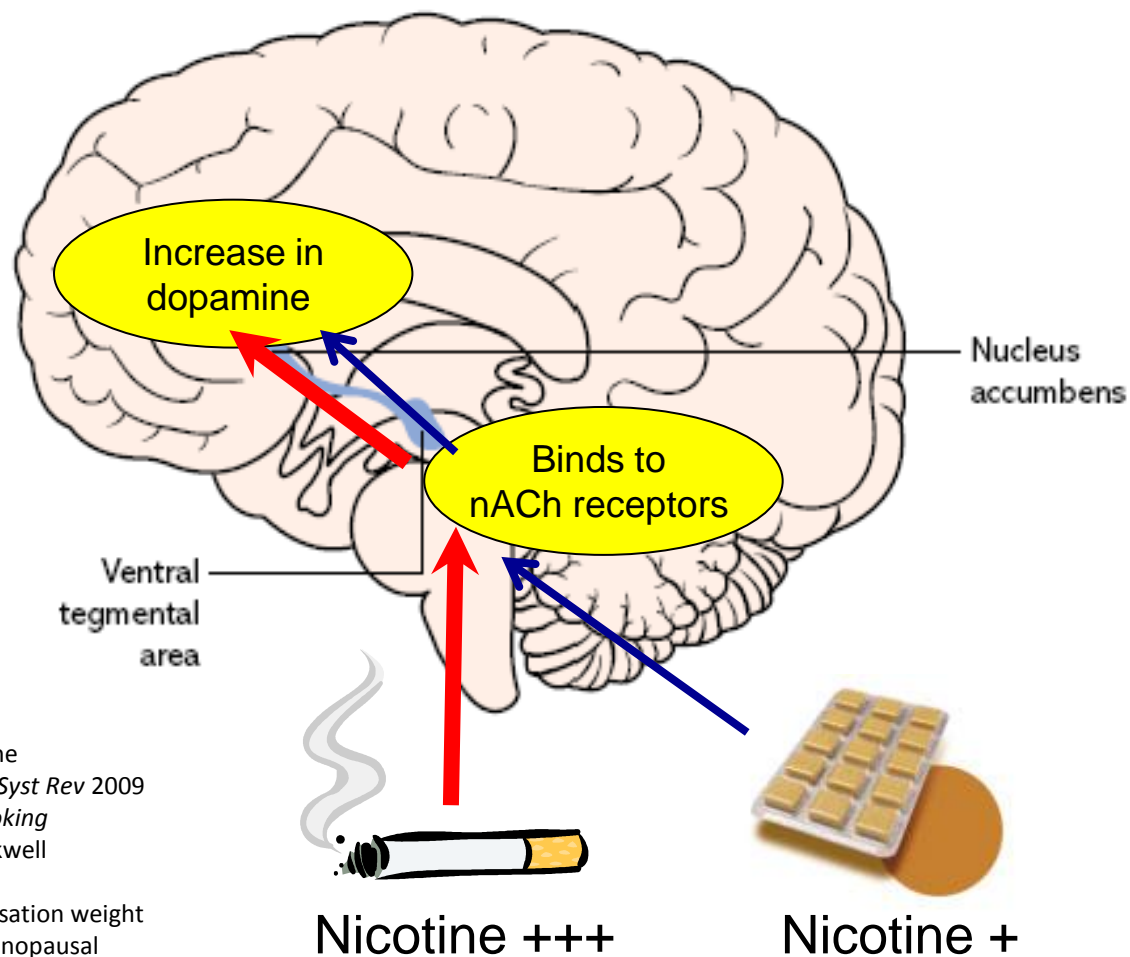
Nicotine Replacement Therapy

- Nicotine Replacement Therapy (NRT) products replace some of the nicotine from cigarette smoking to:
 - Eliminate various harmful elements from smoking
 - Satisfy the need of nicotine
 - Reduce nicotine dependence gradually and finally lead to being tobacco free and nicotine free



NRT: Mechanism of action

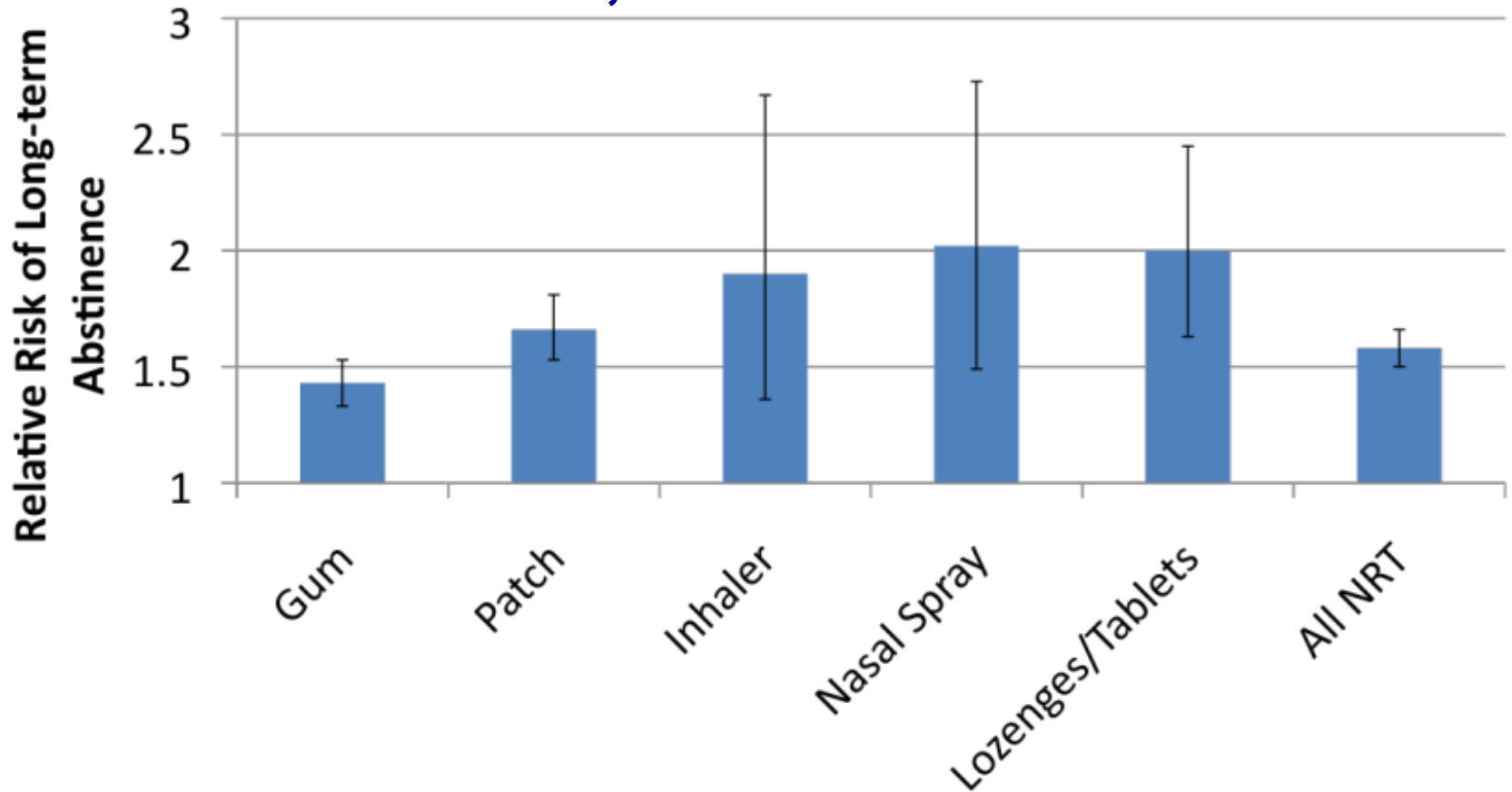
- Reduces severity of withdrawal symptoms¹
- Reduces urge to smoke²
- Delays weight gain³
- Reduces relapse²
- Approximately doubles success rates of long-term abstinence (regardless of type of support used)¹



1. Stead, L. F., Perera, R., Bullen, C., Mant, D. & Lancaster, T. Nicotine replacement therapy for smoking cessation, *Cochrane Database Syst Rev* 2009
2. McEwen, A., Hajek, P., McRobbie, H. and West, R. *Manual of smoking cessation: A guide for counsellors and practitioners*. Oxford: Blackwell Publishing. 2006
3. Allen SS et al. Effect of nicotine replacement therapy on post-cessation weight gain and nutrient intake: a randomized controlled trial of postmenopausal female smokers. *Addict Behav.* 2005. Aug;30(7):1273-80.



Effective, but not a cure



Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008(1)



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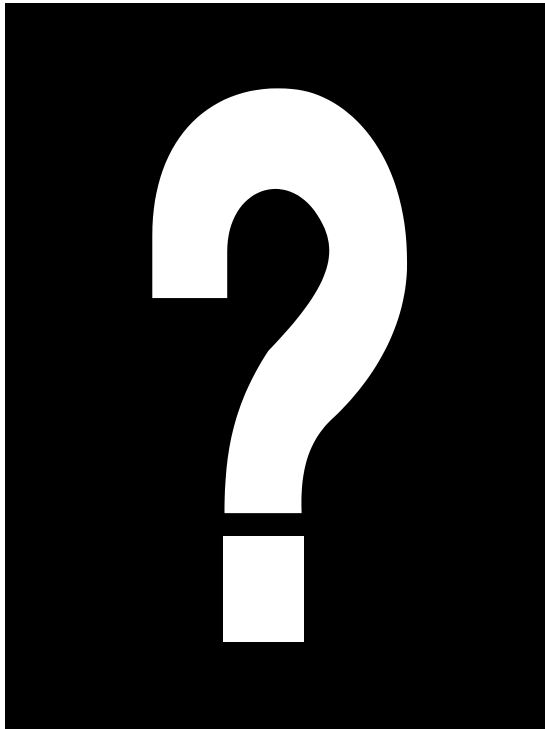
Under-dosing?

- NRT typically provides less than half the nicotine a smoker receives from their tobacco¹
- Even with combination NRT treatment many smokers do not obtain blood nicotine levels comparable with their baseline smoking levels
 - In a trial of combined nicotine patch and inhalator, blood nicotine levels were only 60% of that achieved during ad lib smoking²

1. Johnstone E, Brown K, Saunders C, Roberts K, Drury M, Walton R, et al. Level of nicotine replacement during a quit-smoking attempt. *Nicotine Tob Res* 2004;6(2):377-9
2. Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 2000;160(20):3128-34



In clinical practice



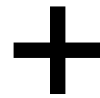
- “Can I recommend a patch and lozenge to be used at the same time?”
- “Is it safe for me to recommend combination therapy?”



Combining NRT Products

- 6 trials comparing combination with single NRT shows advantage of combination use
 - RR = 1.35 (95% CI: 1.11-1.63)

Patch -
provides
background
craving relief

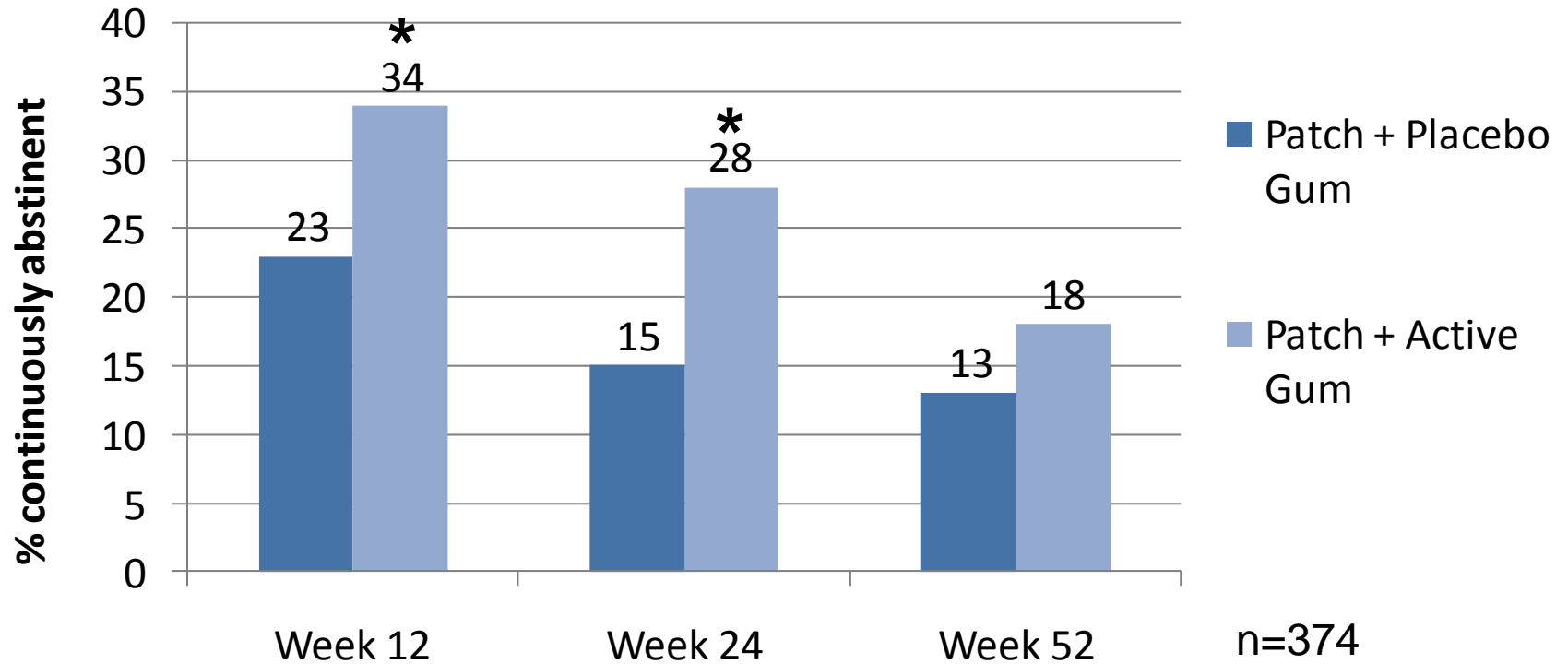


Intermittent dosing product - for control of 'breakthrough craving'

- Mechanism of Action:
 - Higher dose of nicotine
 - Better control of urges to smoke



Patch + Gum



* Significant difference

Kornitzer et al. *Prev Med* 1995.



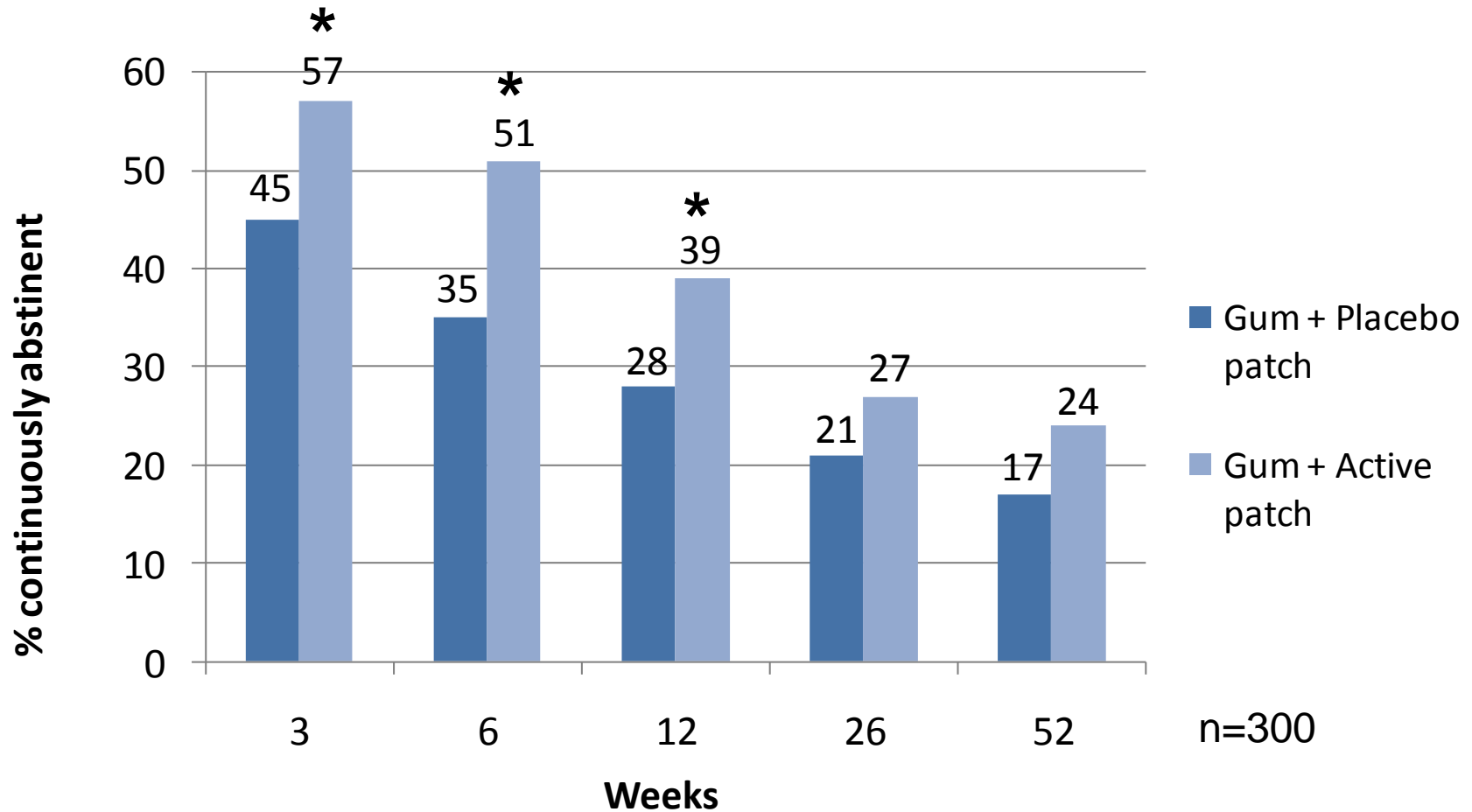
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Gum + Patch



* Significant difference

Puska *et al.* *Tobacco Control*, 1995



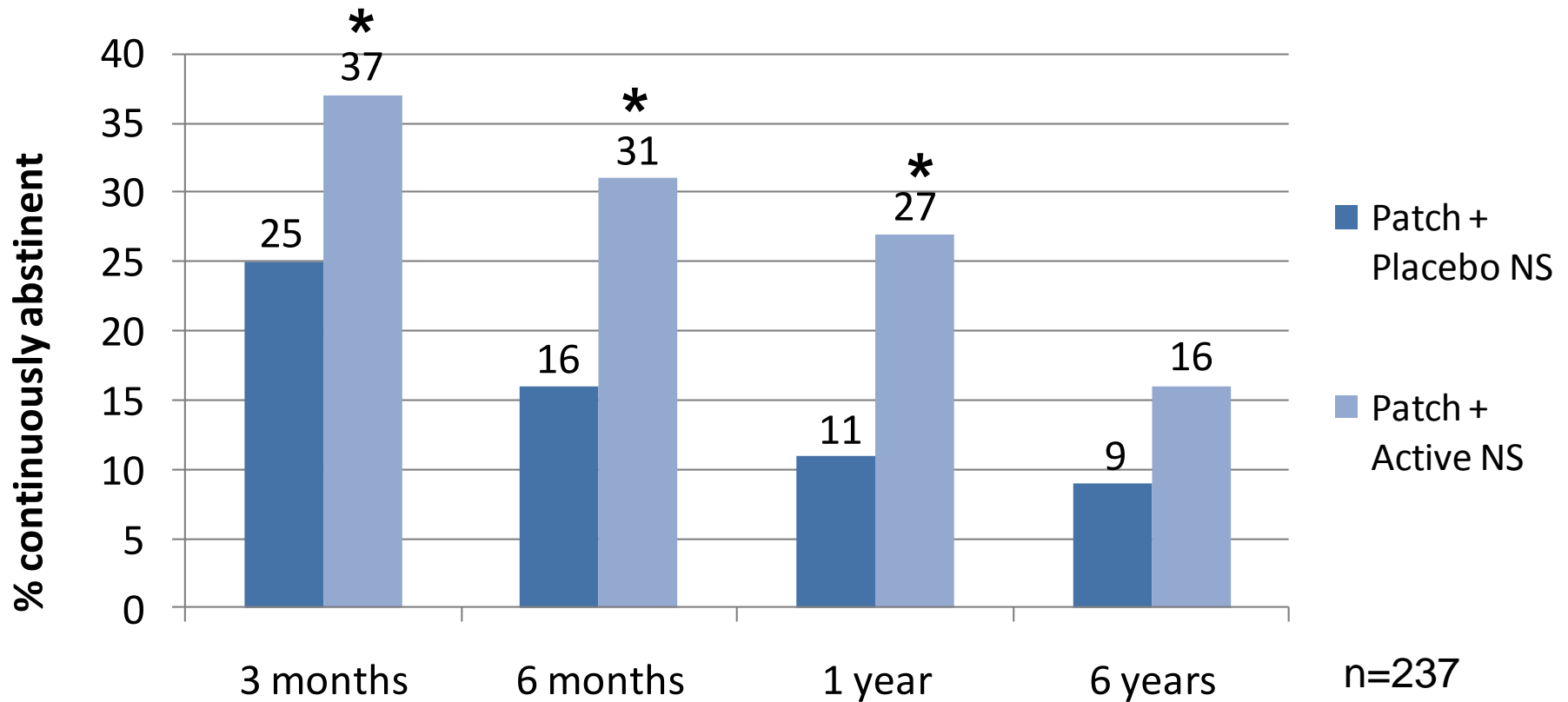
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Patch + Nasal Spray



* Significant difference

Blondal et al. *BMJ* 1999



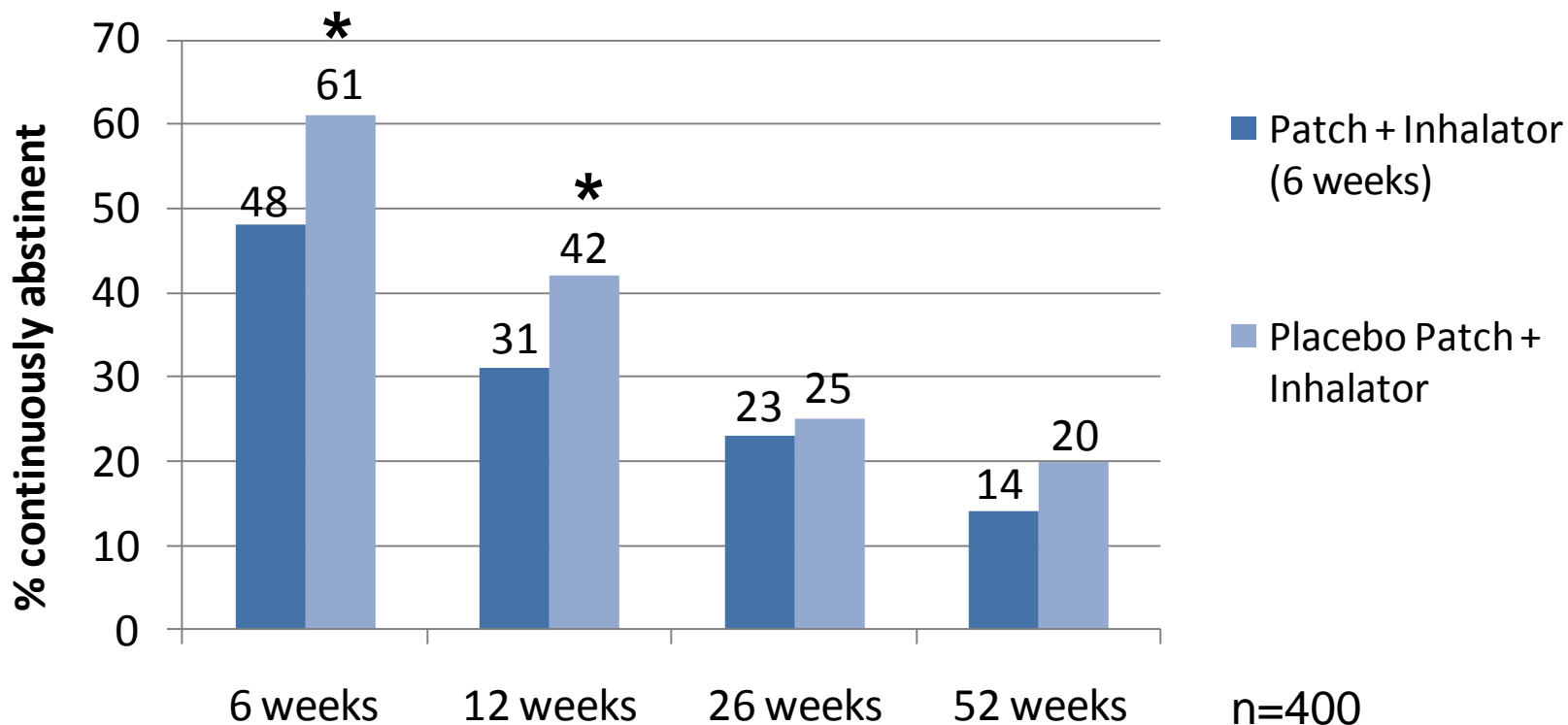
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Patch + Inhalator



* Significant difference

Bohadana et al. Arch. Int Med, 2000 Dec



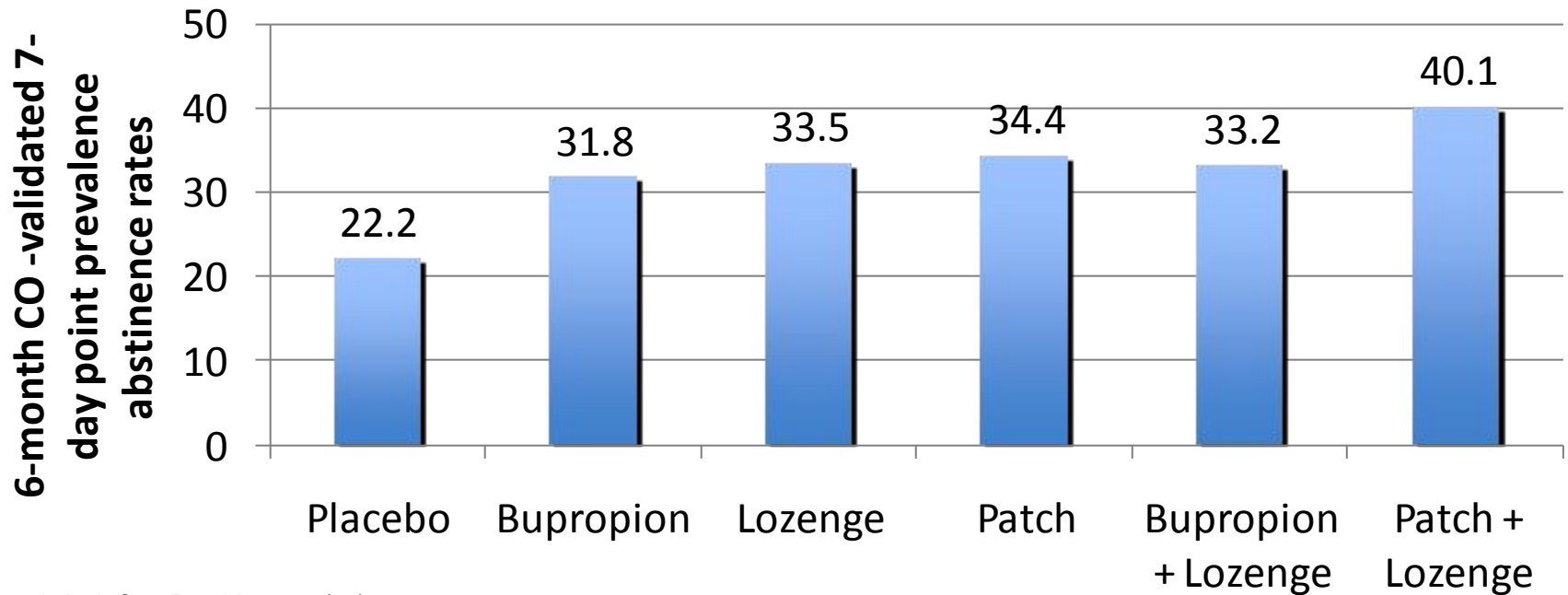
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A study of 'mono' and 'combi' treatment

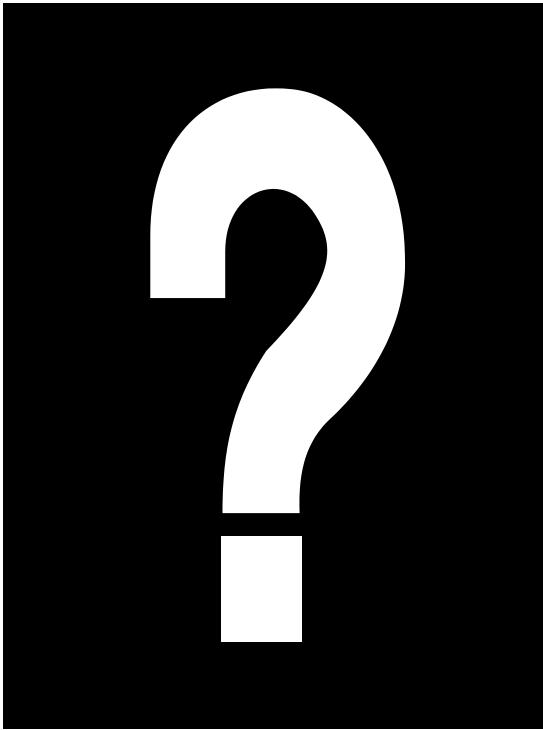


Piper *et al.* *Arch Gen Psychiatry* 66 (11) 2009

- All active treatments were significantly better than placebo
- Only patch + lozenge was better than monotherapy ($p=0.04$)



In clinical practice



- “Can I combine two patches?”



Higher dose patches and craving

- Studies of higher dose patches have produced modest results
 - Seven studies compared higher dose patches (e.g. 44mg/24 hours) with standard doses (21mg/24 hours)¹
 - Overall there was a small increase in long-term quit rates (RR=1.15, 95%CI: 1.01-1.30)¹
- 42 mg patches (vs. 21 mg) were best at **preventing urge to smoke** and an increase in cue-induced withdrawal symptoms after a 10 hour period of abstinence²
- Authors suggest that using 42 mg patch initially in the quit attempt might be helpful²

1. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008(1)

2. Rohsenow DJ, Monti PM, Hutchison KE, Swift RM, MacKinnon SV, Sirota AD, Kaplan GB. High-dose transdermal nicotine and naltrexone: effects on nicotine withdrawal, urges, smoking, and effects of smoking. *Experimental and Clinical Psychopharmacology*. 2007. 15(1)



Safety of combination NRT use

- Incidence of adverse events with combination NRT is not significantly greater than that with single NRT used alone
- Data consistent with safety data showing favourable risk benefit of NRT over wide range of doses and situations
- Smokers capable of titrating their nicotine intake

Risk of overdose

- Smokers have acquired tolerance to large amounts of nicotine
- The adverse effects of nicotine (nausea and vomiting) tend to limit overdose
- Nicotine undergoes first pass metabolism



Varenicline

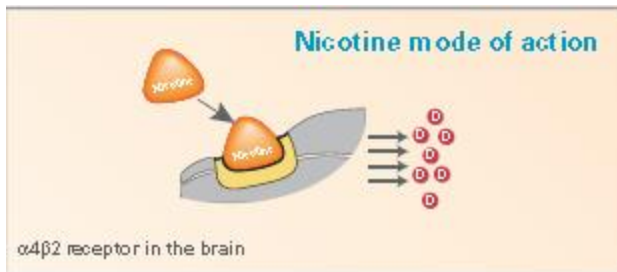
- Varenicline is a partial nicotinic agonist which acts on primarily on alpha4 beta2 nicotinic acetylcholine receptors
- It alleviates withdrawal discomfort, but also to diminish rewarding effects of cigarettes



Mode of action

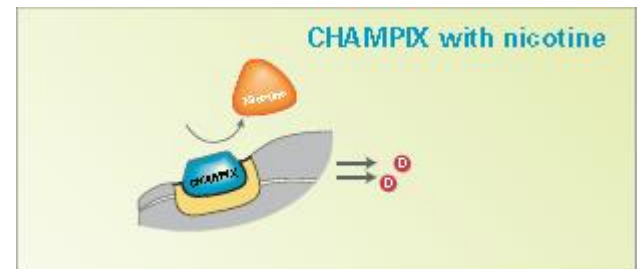
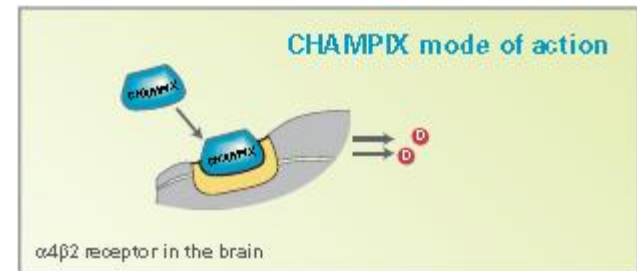
Nicotine

- Binding of nicotine at the $\alpha 4\beta 2$ nicotinic receptor in the VTA is believed to cause release of dopamine at the nAcc



Varenicline

- Varenicline is a compound with dual agonist and antagonist activities.



1. Coe JW *et al.* N Engl J Med 2005;**34**:121-130.



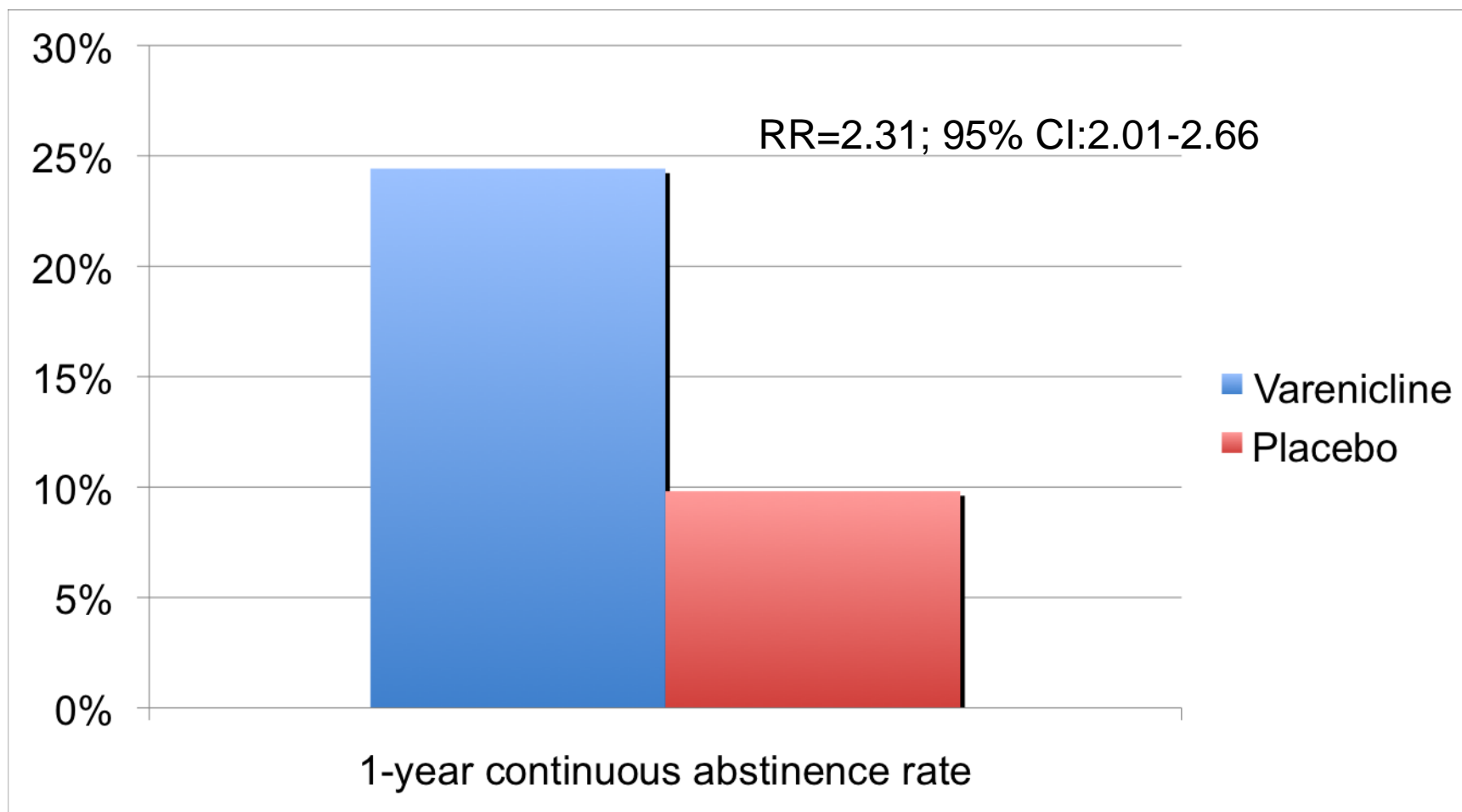
Varenicline and withdrawal

- In studies evaluating its efficacy, patients who lapsed and smoked after the quit date were asked to rate their experience
 - Compared to smokers on placebo, bupropion and nicotine patch, those on **varenicline** derived **less satisfaction** from their cigarettes

Gonzales, Rennard et al. 2006; Jorenby, Hays et al. 2006; Aubin, Bobak et al. 2008; West, Baker et al. 2008



Varenicline: Long-term Quit Rates



Is Champix more effective than:

- Zyban?
 - Yes there is evidence to show that Champix increases long-term quit rates by about 50%
- NRT?
 - No, current data shows no difference in long-term quit rates



In the real world

DW wonders about combining varenicline (CHAMPIX or CHANTIX) and another quit smoking medication:

Can I take Champix and wear the patch at the same time? I cannot seem to quit with just one non-smoking aid at a time. I was successful once before when I took a high daily dosage of Wellbutrin and wore the patch at the same time. Can I wear the patch and take Champix at the same time? -DW

Ads by Google

[Patch](#)

[Quit Smoking Patch](#)

[Patch Link Update](#)

[Patch Link Update](#)

<http://drantoniohowell.com/blog/can-i-take-chantix-and-wear-the-patch-at-the-same-time/>



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Doctor replies

Consult your prescribing healthcare provider

Dear DW,

First let me remind you that whenever you are considering a medication change or combining meds you should consult with your prescribing healthcare provider. You should to avoid combining medications that are potentially

It has not been tested

propose is the fact that Chantix (varenicline) and the

receptors in the brain (alpha4beta2)

whether for the same receptors

same time you will get an increased stimulation of the nicotine receptors. A problem with doing this is that it has not been tested. Furthermore, over-stimulation of the nicotine receptors in your brain can

Nausea, headaches, vomiting, dizziness and flushing are the side effects reported.

Chantix and NRT work on the same receptors

Over stimulation of nAChRs in your brain

<http://drantoniohowell.com/blog/can-i-take-chantix-and-wear-the-patch-at-the-same-time/>



Manufacturers information

Var + 21mg patch
(used for 12 days) had
a greater incidence of
side effects

Pfizer the makers of Chantrel (varenicline) include the following language in their product inserts for varenicline:

Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone. In this study, eight of twenty-two (36%) patients treated with the combination of varenicline and NRT prematurely discontinued treatment due to adverse events, compared to 1 of 17 (6%) of patients treated with NRT and placebo.

8 (36%) of V+NP
users discontinued
early because of AEs
– compared to 1 (6%)
of NP alone or
placebo



Smokers Blogs

“My background is not very simple because the Champix was not enough for me”

“I learnt that you can combine with the Champix and patches, eureka the end of the nightmare! ! ! “

“So I started the patch on June 19 with half a 15mg patch on the advice of my dearest godmother.

The symptoms fade a little but not enough.“

“I gradually increased my patch dosage by half a patch. The goal of course is not being in overdose ... “

“I get a pleasant mix with 1.5 patches, or 22.5 mg, with tablets in addition.”

“Each day as it comes! ! !”

www.stop-tabac.ch/blog/123vivar



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Varenicline + NRT

- Combining varenicline and NRT may in theory
 - improve withdrawal relief
 - help to extinguish smoking rewards
 - lower the risk of lapses translating into relapse
 - NRT may reduce some withdrawal symptoms which are less sensitive to varenicline and vice versa.

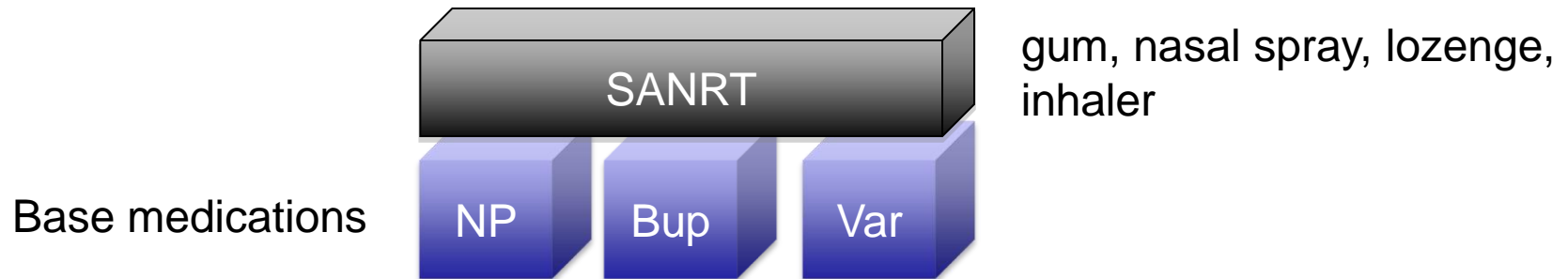


Varenicline + NRT

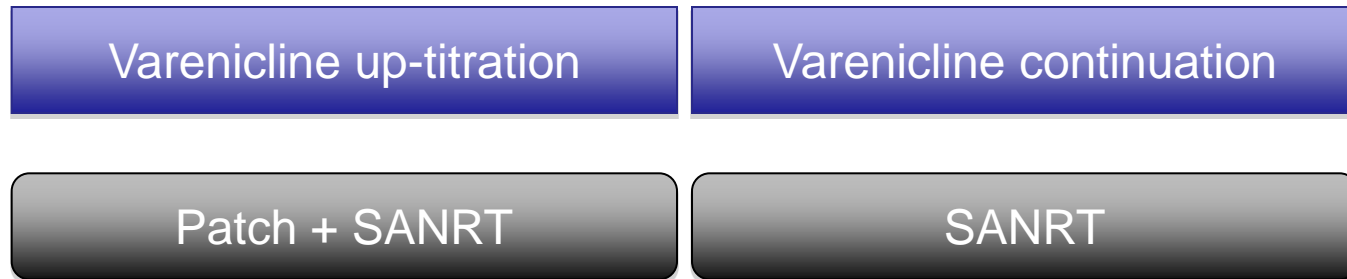
- There are smokers who report no reaction to one of the treatments who may be sensitive to the other and the combination may be of particular benefit to this group



Mayo Clinic



Quit Day



Ebbert, Burke et al. 2009



Mayo results

- One cohort report from an in-patient smoking cessation facility found no difference between large doses of NRT combinations added to varenicline and combinations of similar of-labelling NRT dosing with bupropion added in half the sample.

Ebbert, Burke et al. 2009



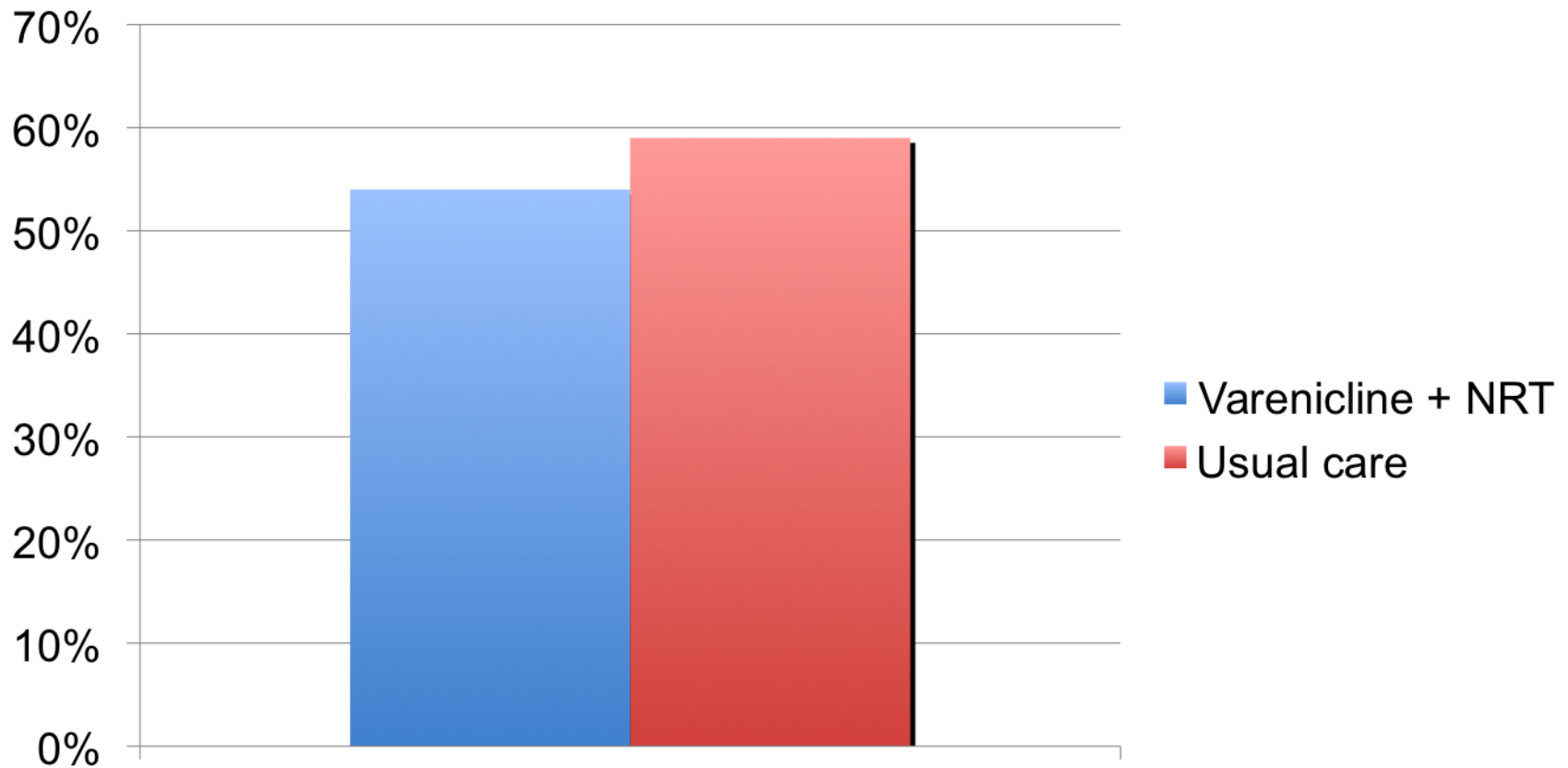
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Real-life use of Var + NRT



6-month 30 day point prevalence abstinence

Ebbert, Burke et al. 2009



Limitations

- As there was no ‘NRT only’ or ‘varenicline only’ group, the results are difficult to interpret, but the report reinforces the need to conduct a randomised ‘proof-of-concept’ study before launching into a large outcome trial.



Safety

- Regarding the safety of combination use of NRT and varenicline a single pre-marketing study showed that smokers using varenicline and transdermal patch for 12 days reported a higher incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue than smokers who used NRT alone (Pfizer Limited 2009).



Safety

- However these symptoms may have been due to varenicline use, as opposed to combined use of varenicline and NRT. Post-marketing data suggests that combined use of varenicline and NRT is well tolerated.

Ebbert, Burke et al. 2009



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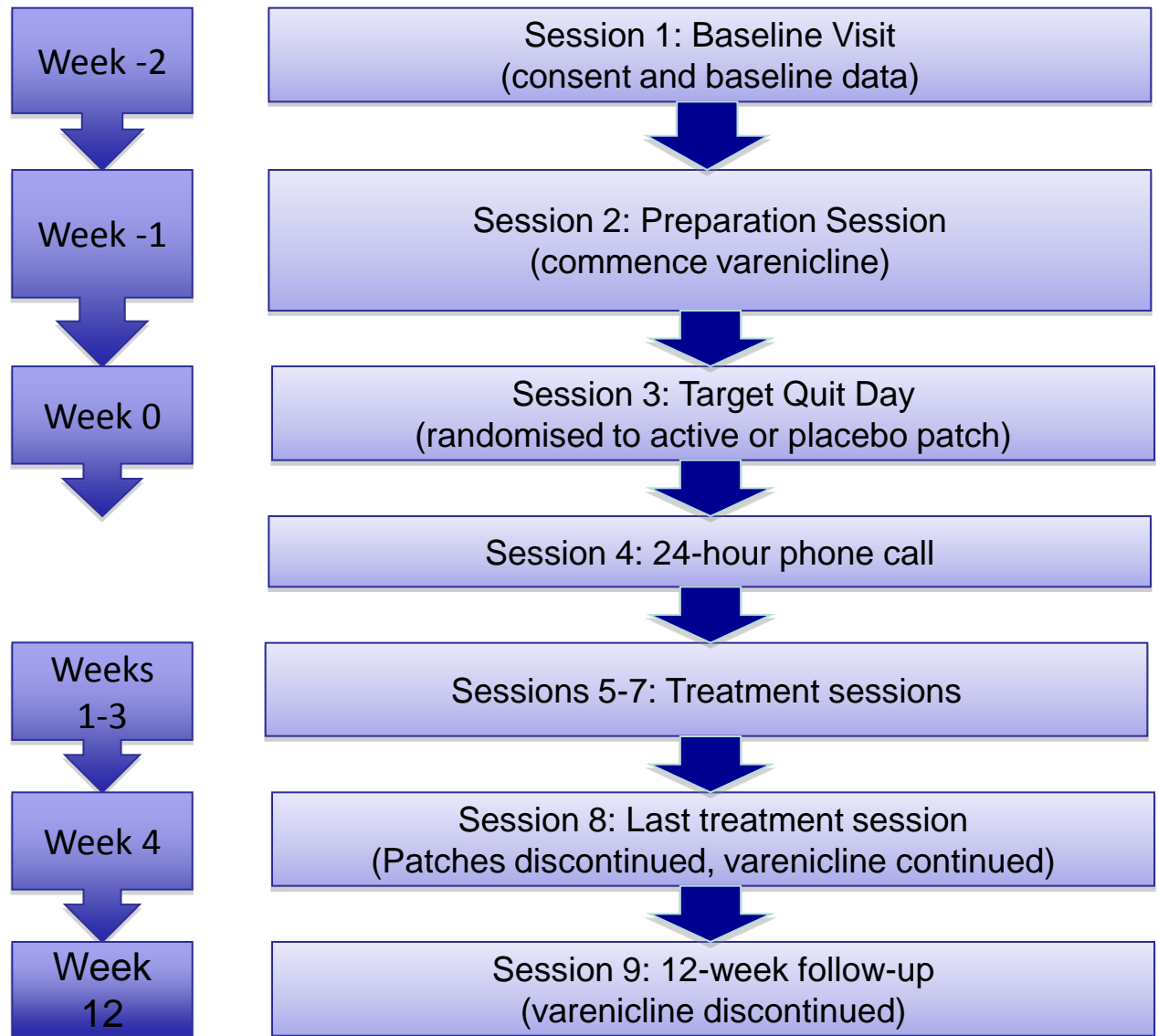
Can I combine Champix with NRT?

- There is no strong evidence suggesting that combining Champix with either of these drugs increases quit rates
- There are no known safety concerns
- Reassure people that they should be just fine using Champix alone. If they need to use an oral NRT for breakthrough craving then this is OK



Combination of
NRT and
varenicline to
increase cessation
of tobacco

CONVICT Study



¡¡GRACIAS!!



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