

Des nouveaux médicaments des addictions? A propos de la varénicline.

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Récepteurs cholinergiques nicotiniques

Varenicline

- Agoniste partiel à forte affinité aux RchN $\alpha 4\beta 2$
- Agoniste complet des RchN $\alpha 7$ mais affinité 1000x moindre

$\alpha 7$ et $\alpha 4\beta 2$ impliqués dans les processus cognitifs (mémoire), dans la régulation d'humeur et dans la dépendance aux substances

Indications potentielles des agonistes nicotiques:

- Schz (fonctions cognitives \uparrow)
- Dépression (\uparrow humeur \rightarrow performances cognitives)
- M. Alzheimer (fonctions cognitives \uparrow)
- Dépendance et/ou abus à l'alcool et/ou aux autres substances

SNC

Sousunités: $\alpha 2$ - $\alpha 10$ et $\beta 2$ -

$\beta 4 \Rightarrow$ combinaisons multiples

Neurotransmetteur endogène :

Ach;

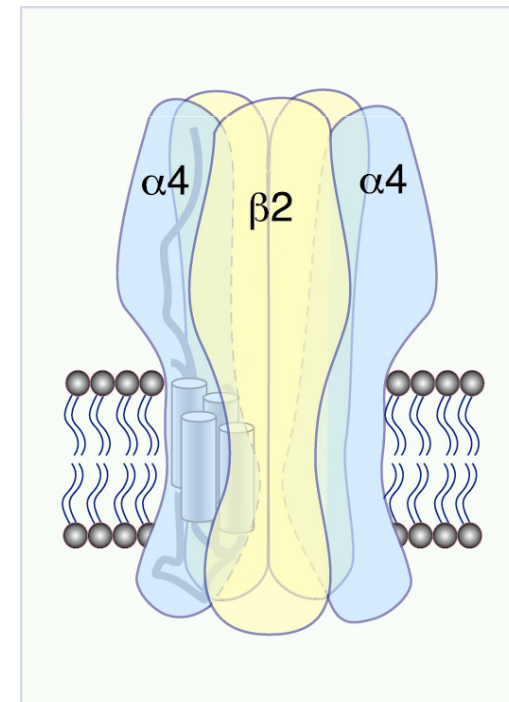
$\alpha 4\beta 2$ RchN prédominant dans le
cerveau

La présence des sous-unités $\beta 2$
sont nécessaires pour

a) Auto-administration de nicotine¹

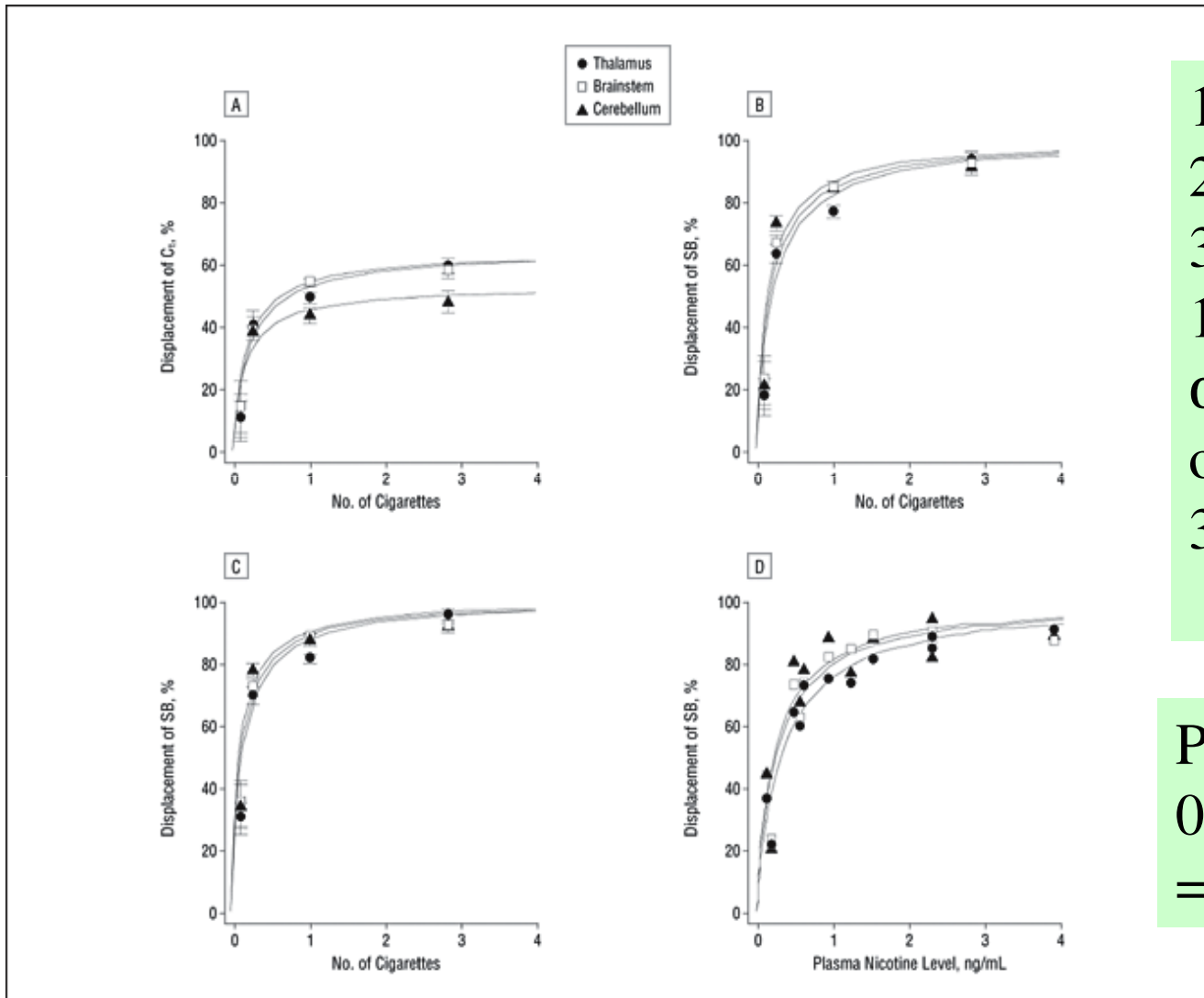
b) Effets cognitifs de la nicotine²

Na⁺ channel



¹Picciotto et al. *Nature* 1998;391:173.²Maskos et al. *Nature*.2005;436:103.

Effects of variable smoking (number of cigarettes) and venous plasma nicotine levels on radiotracer displacement



1 puff 33%
 2 puffs 75 %
 3 puffs 88 %
 1 full cig. 95%
 $\alpha 4\beta 2$ receptor
 occupancy
 3.1 h after smoking

Pl. nicotine of
 0.87 ng/ml (0.13 cig.)
 = 50% occupancy

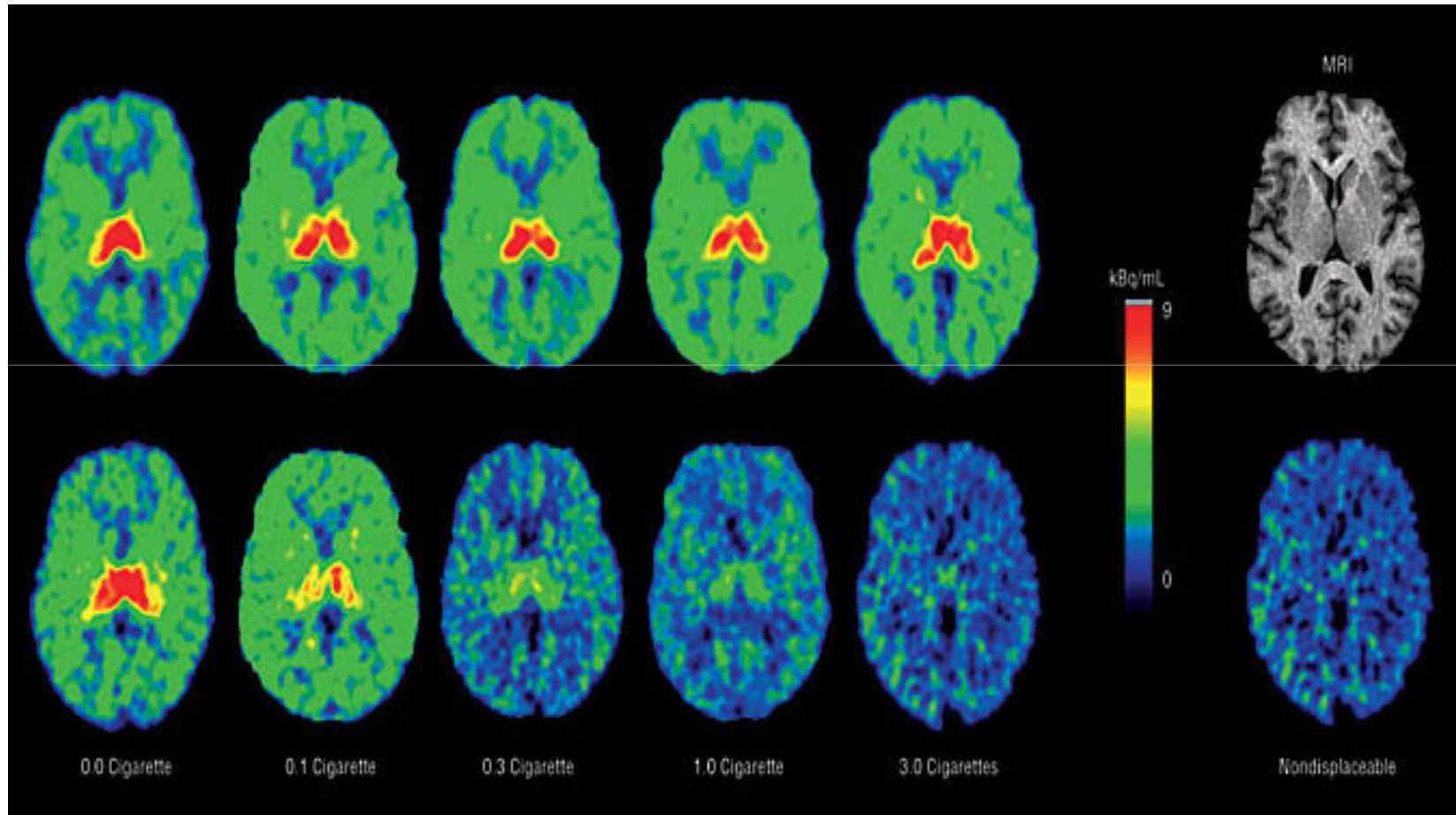
Brody, A. L. et al. Arch Gen Psychiatry 2006;63:907-914.

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$\alpha 4\beta 2$ NAcHR binding

2-[^{18}F]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



Brody, A. L. et al. Arch Gen Psychiatry 2006;63:907-914.

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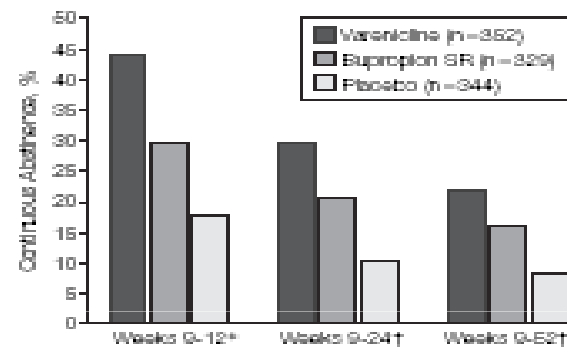
Cytisine

- Cytise jaune
- 2ième guerre mondiale: utilisée comme substitut de tabac
- Commercialisée à l'Europe de l'Est
- Forte affinité aux récepteurs nicotiques $\alpha 4\beta 2$
- Pas de développement pharmacologique: pas d'étude de phase I - III

Etter JF Arch Int Med 2006;166:1553-9.

Authors	<i>Doses (mg/day) & Odds ratios (95 % IC) vs Placebo</i>			
	Varenicline			Bupropion
Nakamura et al. 2007 Japan	<i>0.25 BID</i> 1.88 (1.14-3.12)	<i>0.5 BID</i> 1.94 (1.17-3.22)	<i>1 BID</i> 2.98 (1.78-4.99)	
Tsai et al 2007 Korea & Taiwan			<i>1 BID</i> 3.22 (1.89-5.47)	
Nides et al. 2006, USA	<i>0.3 BID</i> NS	<i>1 OD</i> 2.97 (1.63-5.4)	<i>1 BID</i> 4.71 (2.6-8.53)	<i>300</i> 2.53 (1.38-4.63)
Gonzales et al. 2006, USA			3.85 (2.7-5.5)	1.93 (1.4-2.68)
Jorenby et al. 2006, USA			3.85 (2.69-5.5)	1.9 (1.38-2.62)

Figure 2. Continuous Abstinence Rates

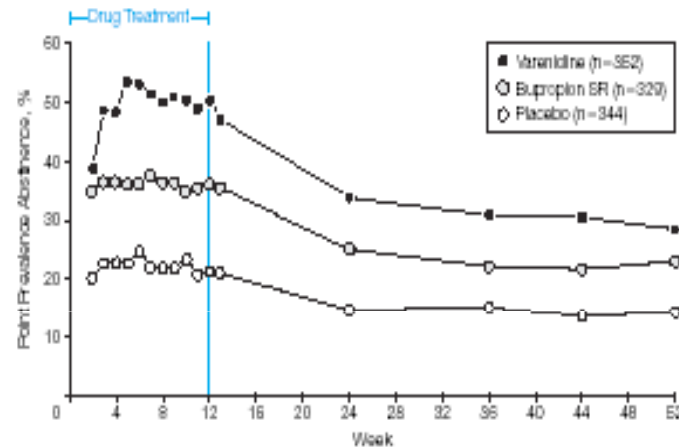


The Ns shown in the key are the denominators used for all 3 periods. $P < .001$ for all comparisons except varenicline vs sustained-release bupropion (bupropion SR) at weeks 9 through 24 ($P = .007$), varenicline vs bupropion SR at weeks 9 through 52 ($P = .057$), and bupropion SR vs placebo at weeks 9 through 52 ($P = .001$).

†Abstinence confirmed by measurement of exhaled carbon monoxide.

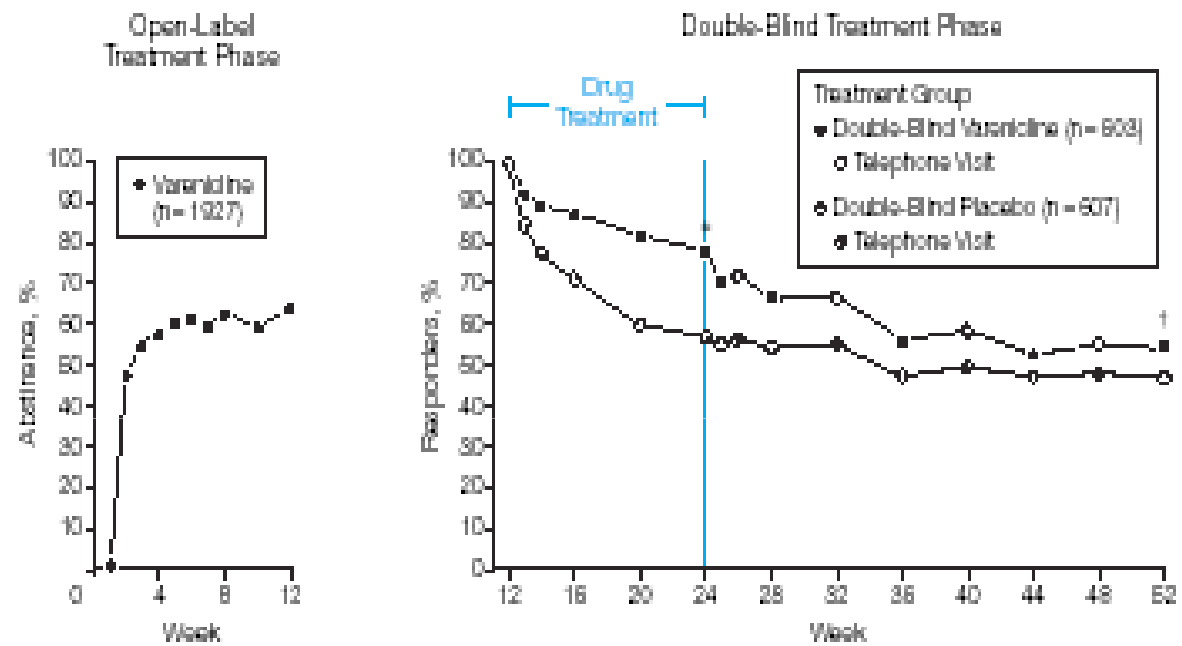
‡Clinic and telephone visits; abstinence confirmed by measurement of exhaled carbon monoxide at clinic visits.

Figure 3. 7-Day Point Prevalence Abstinence



The Ns shown in the key are the denominators used for all time points. The 7-day point prevalence rate of abstinence at week 12 was 50.3% for the varenicline group vs 21.2% for the placebo group ($P < .001$) and 35.9% for the sustained-release bupropion (bupropion SR) group ($P < .001$). At week 24, 33.5% of the varenicline group were abstinent vs 14.5% of the placebo group ($P < .001$) and 24.9% of the bupropion SR group ($P = .01$). At week 52, 28.1% of the varenicline group were abstinent vs 14% of the placebo group ($P < .001$) and 22.8% of the bupropion SR group ($P = .13$).

Figure 2. Seven-Day Point Prevalence of Abstinence



* $P < .001$.

† $P = .01$.

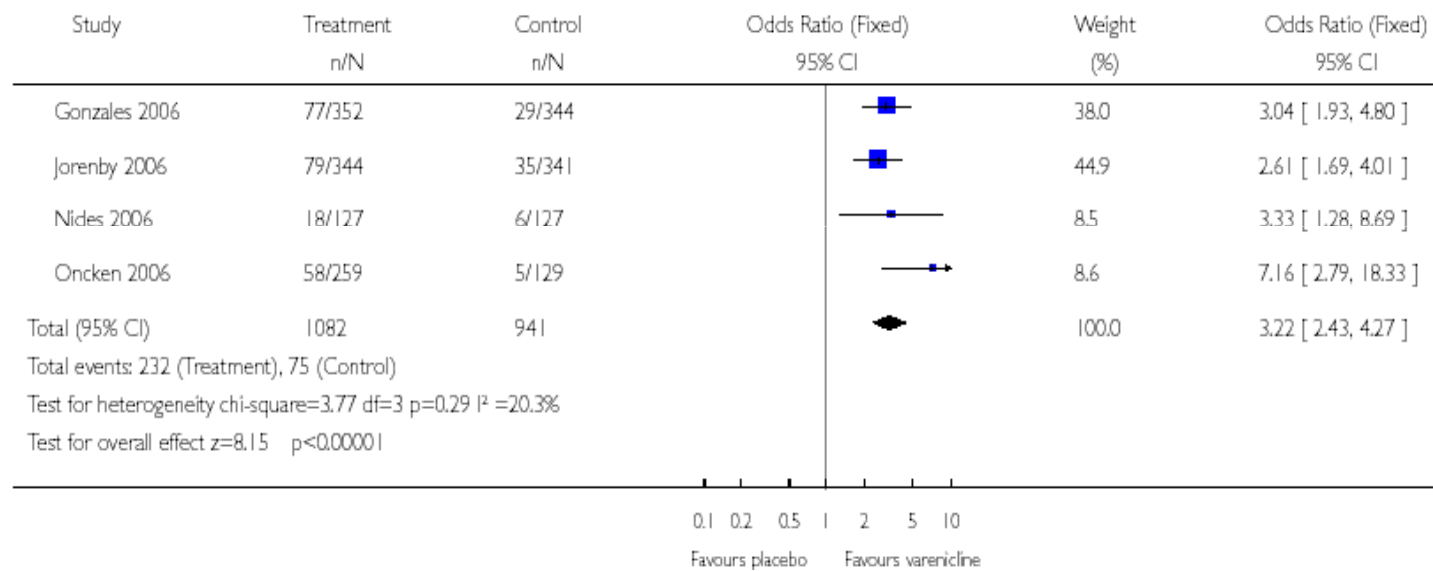
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Varenicline (1.0mg 2/d) vs placebo, Outcome 01 Continuous abstinence at 52 weeks

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 01 Varenicline (1.0mg 2/d) vs placebo

Outcome: 01 Continuous abstinence at 52 weeks



Analysis 04.01. Comparison 04 Most frequent adverse effects, Outcome 01 Nausea

Nausea			
Study	Placebo n/N (%)	Varenicline n/N (%)	Bupropion n/N (%)
Gonzales 2006	29/344 (8.4)	98/349 (28.1)	41/329 (12.5)
Jorenby 2006	33/340 (9.7)	101/343 (29.4)	25/340 (7.4)
Nides 2006	23/123 (18.7)	65/125 (52.0)	27/126 (21.4)
Oncken 2006	18/121 (14.9)	97/253 (38.3) 45/129 (34.9) titrated 52/124 (41.9) non-titrated	

Analysis 04.03. Comparison 04 Most frequent adverse effects, Outcome 03 Abnormal dreams

Abnormal dreams			
Study	Placebo n/N (%)	Varenicline n/N (%)	Bupropion n/N (%)
Gonzales 2006	19/344 (5.5)	36/349 (10.3)	18/329 (5.5)
Jorenby 2006	12/340 (3.5)	45/343 (13.1)	20/340 (5.9)
Nides 2006	10/123 (8.1)	19/125 (15.2)	15/126 (11.9)
Oncken 2006	6/121 (5.0)	46/253 (18.2) 25/129 (19.4) titrated 21/124 (16.9) non-titrated	
Reeves 2006	9/126 (7.1)	57/251 (22.7)	

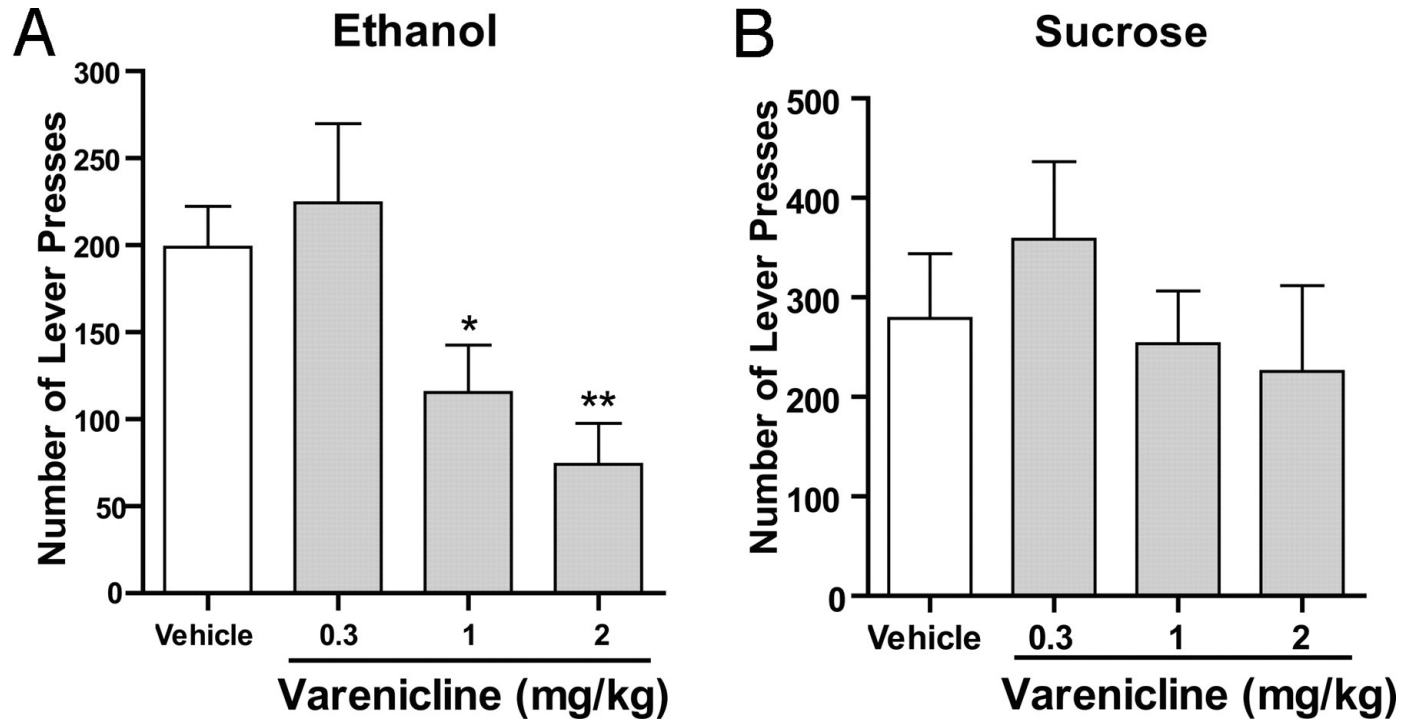
Placebo or varenicline 1 mg BID for 52 weeks

*Table 4. Most frequent all-causality treatment-emergent adverse events**

Adverse event	Varenicline mg BID (<i>n</i> = 251) <i>n</i> (%)	Placebo (<i>n</i> = 126) <i>n</i> (%)
Gastrointestinal disorders		
Nausea	101 (40.2)	10 (7.9)
Dyspepsia	33 (13.1)	3 (2.4)
Constipation	31 (12.4)	9 (7.1)
Flatulence	31 (12.4)	12 (9.5)
Vomiting	17 (6.8)	2 (1.6)
Infections and infestations		
Upper respiratory tract infection	34 (13.5)	12 (9.5)
Sinusitis	17 (6.8)	8 (6.3)
Influenza	15 (6.0)	3 (2.4)
Psychiatric disorders		
Abnormal dreams	57 (22.7)	9 (7.1)
Insomnia	48 (19.1)	12 (9.5)
Nervous system disorders		
Dysgeusia	27 (10.8)	3 (2.4)
Dizziness	19 (7.6)	6 (4.8)
Musculoskeletal and connective tissue disorders		
Arthralgia	18 (7.2)	7 (5.6)
Back pain	16 (6.4)	6 (4.8)
All other system organ classes		
Weight increase	17 (6.8)	5 (4.0)
Hypertension	15 (6.0)	5 (4.0)
Increased appetite	13 (5.2)	4 (3.2)

*Only includes events that occurred at an incidence (all causalities) of $\geq 5\%$ in the varenicline treatment group *and* were more frequent in varenicline-treated than placebo-treated subjects

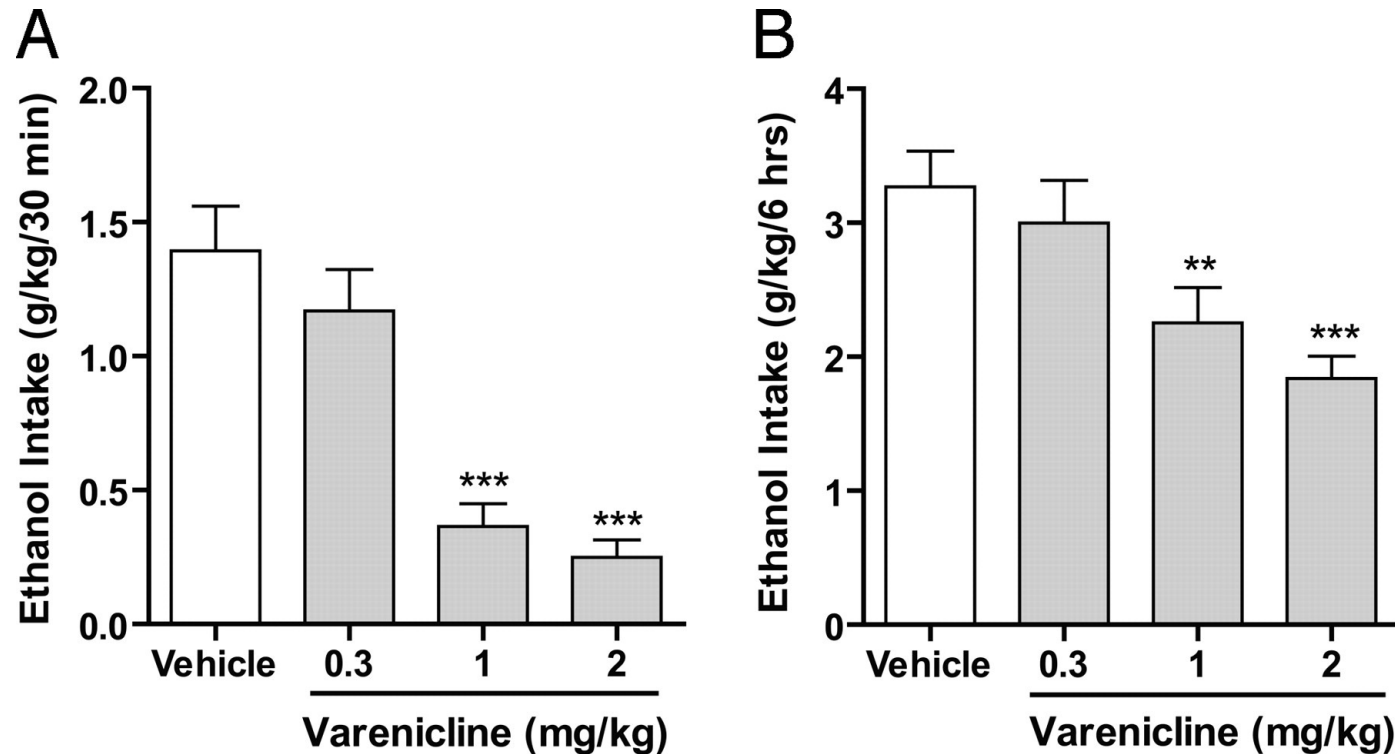
Fig. 1. Varenicline decreased ethanol but not sucrose seeking



Steensland, Pia et al. (2007) Proc. Natl. Acad. Sci. USA 104, 12518-12523

Varenicline decreased ethanol but not sucrose seeking. One and 2 mg/kg significantly and dose-dependently inhibited active lever presses for 10% ethanol (A) but not 5% sucrose (B).

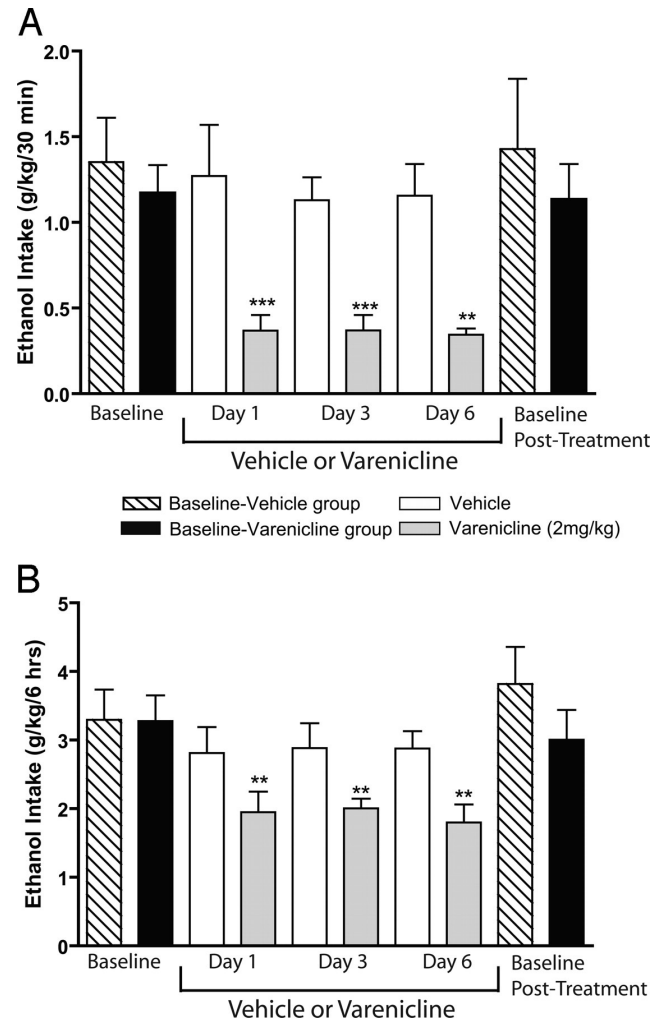
Fig. 4. Varenicline significantly decreases ethanol consumption in rats chronically consuming large amounts of ethanol (intermittent access to 20% ethanol)



Steensland, Pia et al. (2007) Proc. Natl. Acad. Sci. USA 104, 12518-12523

Varenicline significantly decreases ethanol consumption in rats chronically consuming large amounts of ethanol (intermittent access to 20% ethanol). Varenicline (0.3–2 mg/kg s.c.) was administered 30 min before the start of the drinking session. Varenicline (1 and 2 mg/kg) significantly decreased ethanol consumption 30 min (A) and 6 h (B) after the onset of drinking.

Fig. 5. Chronic administration of varenicline significantly decreases ethanol consumption in rats chronically consuming ethanol (intermittent access to 20% ethanol)



Steensland, Pia et al. (2007) Proc. Natl. Acad. Sci. USA 104, 12518-12523

Patch nicotinique et consommation d'alcool

1. Alcohol Effects Scale (AES)

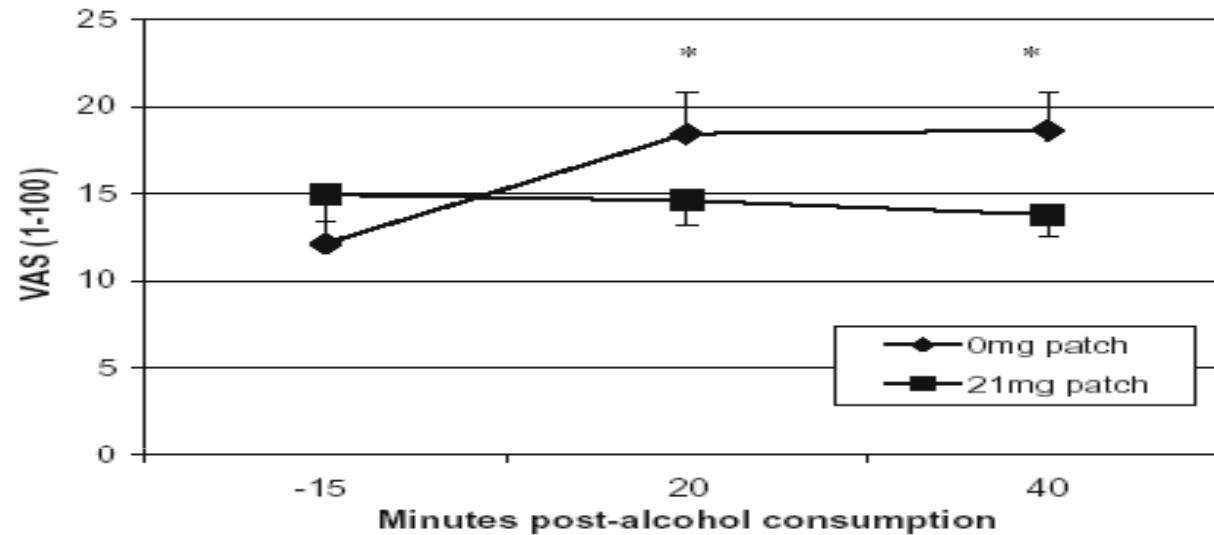


Fig. 1 Mean visual analogue scale ratings (VAS 1–100) for AES during the priming drink period for each transdermal nicotine replacement condition (0 vs 21 mg/day). AES is a mean score of *high, like, rush, feel-good, intoxicated*. * $p < 0.05$ paired comparisons for 0 mg vs 21 mg/day nicotine patch within a timepoint

2. Patch nicotinique (21 mg) a retardé le prise d'alcool *ad lib* après la première dose d'alcool
(1ère h - PN: 6 min, PP: 3 min; 2ième h - PN: 13 min PP: 7 min)

1 [Study of Mood Effects of Varenicline \(Chantix\) in Depressed Outpatient Smokers](#)

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Conditions: Depressive Disorder; Smoking; Antidepressive Agents

2 [The Effects of Varenicline on Cognitive Function in Patients With Schizophrenia](#)

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Condition: Schizophrenia

3 [Cognitive Effects of Mecamylamine and Varenicline in Schizophrenia](#)

·
condition: Cognition in Schizophrenia

4 [Effectiveness and Safety of Varenicline in Smokers With Cardiovascular Disease Who Wish to Quit Smoking](#)

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Condition: Smoking Cessation

5 [Naltrexone and Varenicline: Weight Gain and Tolerability in Cigarette Smokers](#)

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Conditions: Smoking; Nicotine Dependence

6 [Varenicline Adjunctive Treatment in Schizophrenia](#)

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Conditions: Schizophrenia; Schizoaffective Disorder

7 [Mood and Anti-Craving Effects of Varenicline in Psychiatric Inpatients](#)

·
Conditions: Smoking; Depressive Disorder

8 [Multiple Dose, Dose Escalation Study of Varenicline Controlled Release Formulation in Adult Smokers](#)

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Condition: Smoking Cessation

9 [A Phase I Study to Evaluate the Pharmacokinetics of Multiple Doses of Varenicline in Healthy Adolescent Smokers](#)

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Condition: Smoking Cessation

1 [Post Marketing Surveillance Study to Observe Safety and Efficacy of Champix® Tablets](#)

0
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Condition: Smoking Cessation

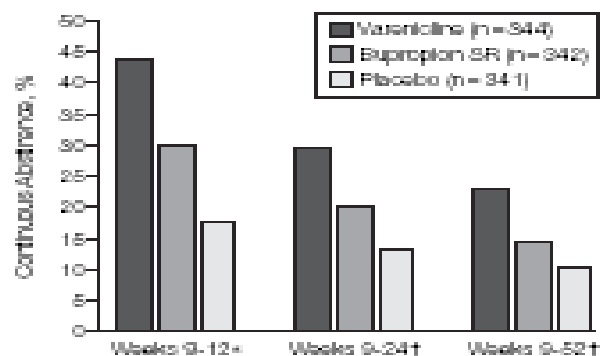
1 [Smoking Cessation in Subjects With Mild-to-Moderate Chronic Obstructive Pulmonary Disease \(COPD\).](#)

1
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Condition: COPD

Conclusions

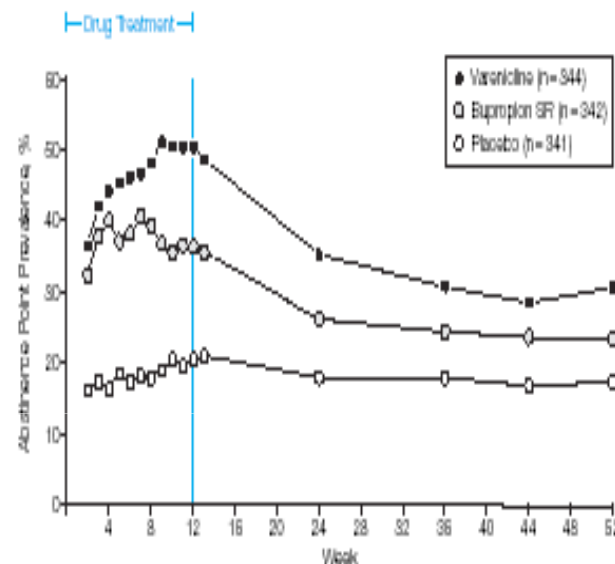
- Effet thérapeutique principale à compléter par les effets thérapeutiques parallèles (secondaires **en opposition aux effets indésirables**)
- Bases théoriques et neurobiologiques vont dans le sens des interventions pharmacologiques et non-pharmacologiques +/- uniformes pour des addictions multiformes ← similitudes neurbiologiques/de polymorphismes génétiques/de traits de personnalité, etc
- La recherche publique doit évaluer ces thérapeutiques

Figure 2. Continuous Smoking Abstinence Rates



*Carbon monoxide level confirmed at clinic visits.
 †Clinic and telephone visits.
 Bupropion SR indicates sustained-release bupropion.
 For weeks 9-12: varenicline vs placebo, $P < .001$; varenicline vs bupropion SR, $P < .001$; and bupropion SR vs placebo, $P = .001$. For weeks 9-24: varenicline vs placebo, $P < .001$; varenicline vs bupropion SR, $P = .003$; and bupropion SR vs placebo, $P = .01$. For weeks 9-52: varenicline vs placebo, $P < .001$; varenicline vs bupropion SR, $P = .004$; and bupropion SR vs placebo, $P = .08$.

Figure 3. Smoking Abstinence Point Prevalence Verified by Carbon Monoxide Level at 7 Days



Bupropion SR indicates sustained-release bupropion.

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