A translational approach to discover novel therapeutic strategies for nicotine addiction

Bernard Le Foll, MD PhD CCFP

Head, Alcohol Research and Treatment Clinic, Ambulatory Care and Structured Treatments, CAMH.

Head, Translational Addiction Research Laboratory, Campbell Family Mental Health Research Institute, CAMH.

Associate Professor, Department of Family and Community Medicine, Pharmacology, Psychiatry and Institute of Medical Sciences, University of Toronto

camh
Centre for Addiction and Mental Health

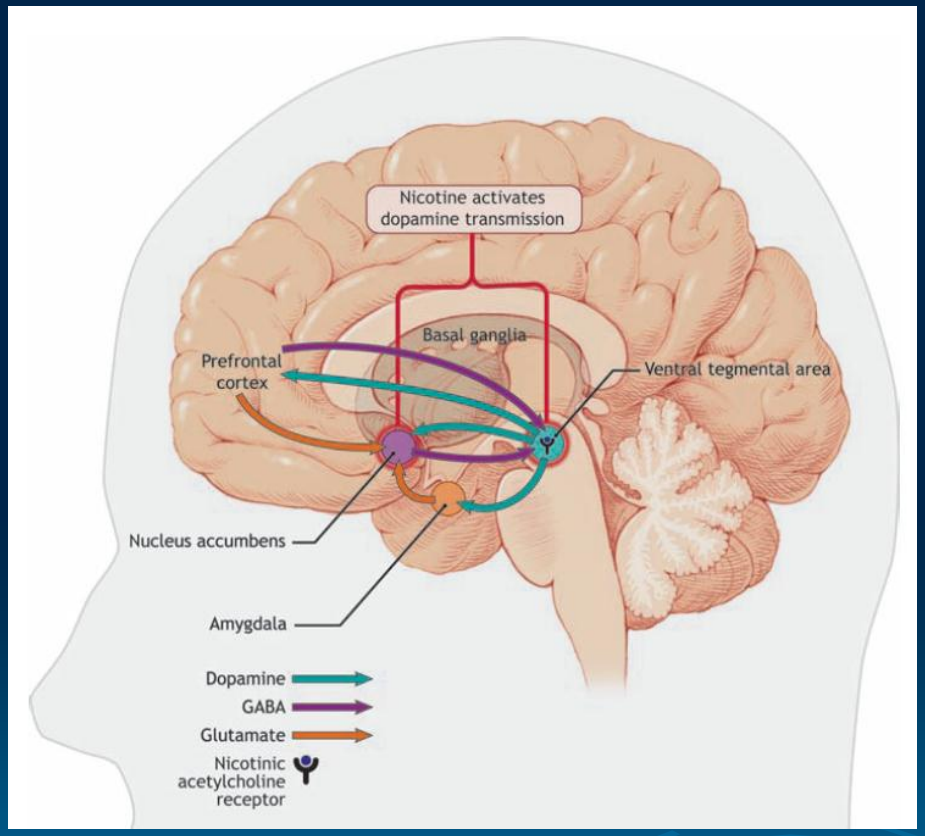
UNIVERSITY OF TORONTO

Disclosures

Dr Le Foll' Research support:
CAMH
Ontario Ministry of Innovation
Canadian Fondation for Innovation,
Canadian Tobacco Control Research Initiative
Pfizer GRAND Award 2008, 2009, 2010, 2011
Pfizer Cardio-vascular Research Award
CIHR training program
OPGRC
Ontario Lung Association
Heart and Stroke Foundation
CIHR
NIH-NIDA

Dr Le Foll' Consulting: Speaker fees and salary support from Pfizer, speaker fees from Mylan pharmaceutical. Consulting for Richter Pharmaceuticals and Lundbeck

Outline



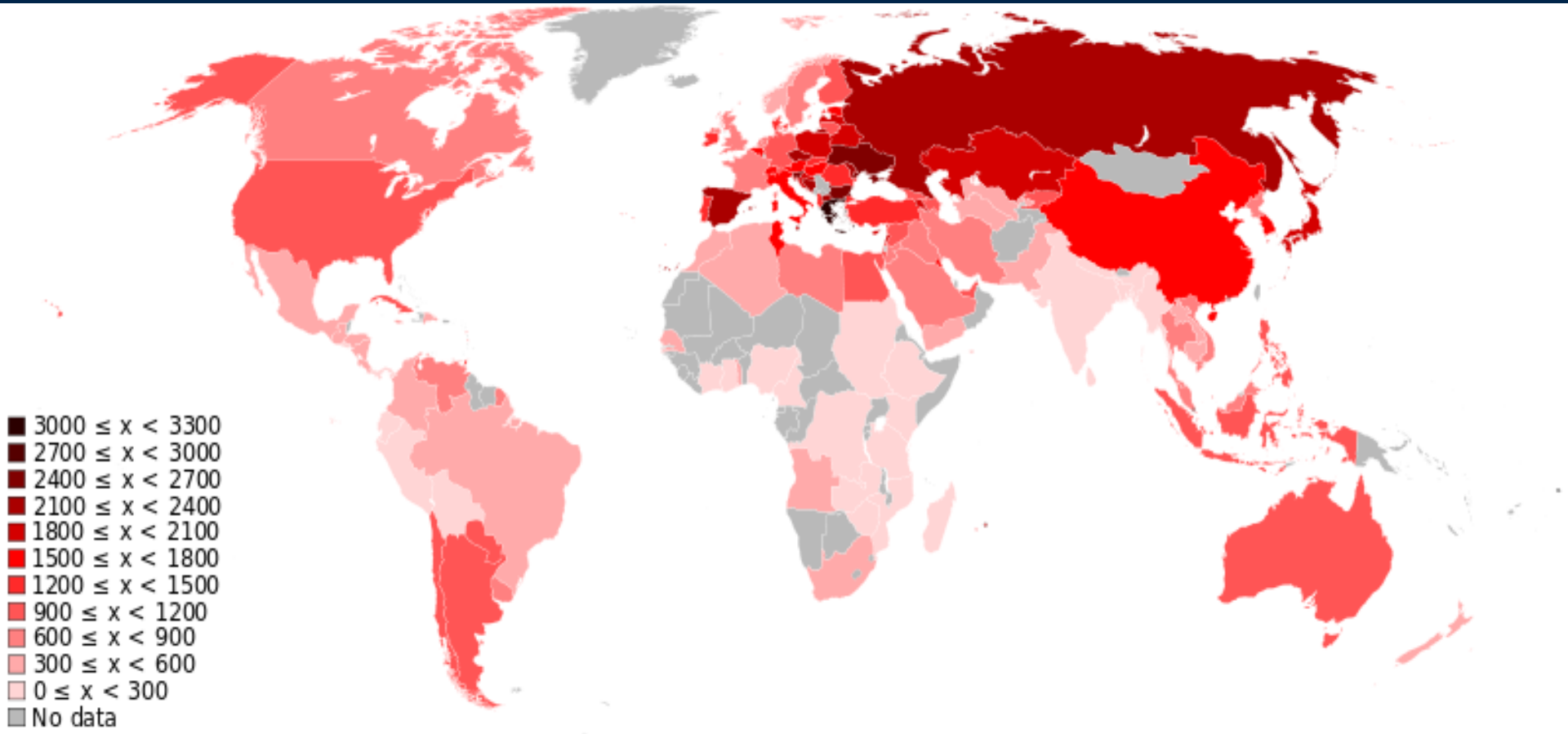
Le Foll, 2007 *CMAJ*

- Epidemiology/Burden of disease

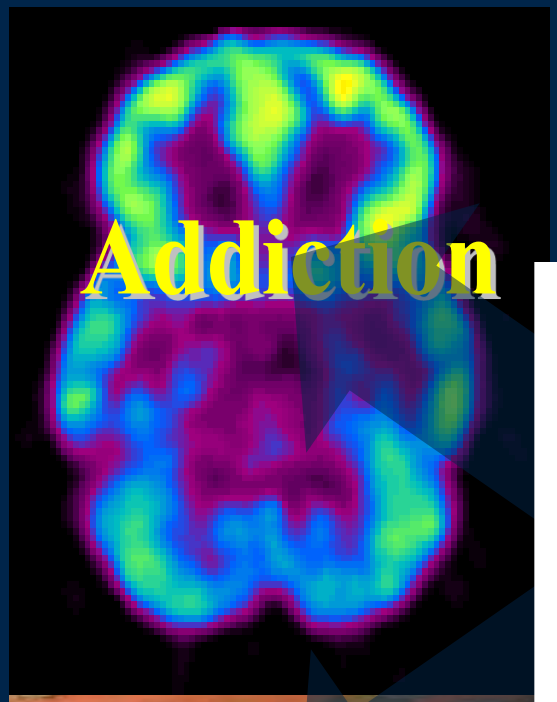
-Current pharmacological approaches (NRT, Zyban, Champix)

-Parallel between Human and Animals (CB1/Insula)

Tobacco Use Worldwide



Expressed in number of cigarettes smoked per year; From WHO



TOBACCO

Current Use Ranking: Alcohol>Tobacco>Cannabis>Illicit Drug

	Prevalence (%) of past-year use
Alcohol	65.44
Tobacco	27.66
Sedatives	1.24
Tranquilizers	0.93
Painkillers	1.81
Stimulants	0.49
Marijuana	4.07
Cocaine/crack	0.56
Hallucinogens	0.57
Solvents/ inhalants	0.11
Heroin	0.03

From Grant et al, 2001, NESARC data

Use, Abuse and Dependence

Table 2. Past-Year Liability for Various Types of Substance Dependence, Based on 200 Million United States Adults ≥18 Years of Age (2001–2002)[a]

	Prevalence (%) of past-year use	Number of individuals with past-year use	Percentage of past-year users with past-year dependence	Number of individuals with past-year dependence
Alcohol	65.44	130,880,000	5.82	7,617,216
Tobacco	27.66	55,320,000	46.13	25,519,116
Sedatives	1.24	2,480,000	5.42	134,416
Tranquilizers	0.93	1,860,000	5.04	93,744
Painkillers	1.81	3,620,000	6.3	228,060
Stimulants	0.49	980,000	14.34	140,532
Marijuana	4.07	8,140,000	7.96	647,944
Cocaine/crack	0.56	1,120,000	23.91	267,792
Hallucinogens	0.57	1,140,000	2.67	30,438
Solvents/ inhalants	0.11	220,000	1.04	2,288
Heroin	0.03	60,000	26.96	16,176

[a]The data are from Wave I of the National Epidemiologic Survey on Alcohol and Related Conditions (2001–2002; Grant et al., 2011).

Estimated Economic Cost to US Society from Substance Abuse and Addiction:

Alcohol:	$185 billion/year
Illegal drugs:	$181 billion/year
Tobacco:	$158 billion/year
Total:	**$524 billion/year**

Surgeon General's Report, 2004; ONDCP, 2004; Harwood, 2000.

Ranking of overall harm based on the mortality

	ILLICIT DRUG	ALCOHOL	TOBACCO
Africa	28 000	213 000	158 000
Americas	61 000	279 000	802 000
Europe	33 000	538 000	1 605 000
Eastern Mediterranean	15 000	16 000	186 000
Southeast Asia	17 000	229 000	1 035 000
Western Pacific	44 000	526 000	978 000
Total	197 000	1 804 000	4 800 000

From Degenhard et al, 2012, Lancet

Current Pharmacological Approaches

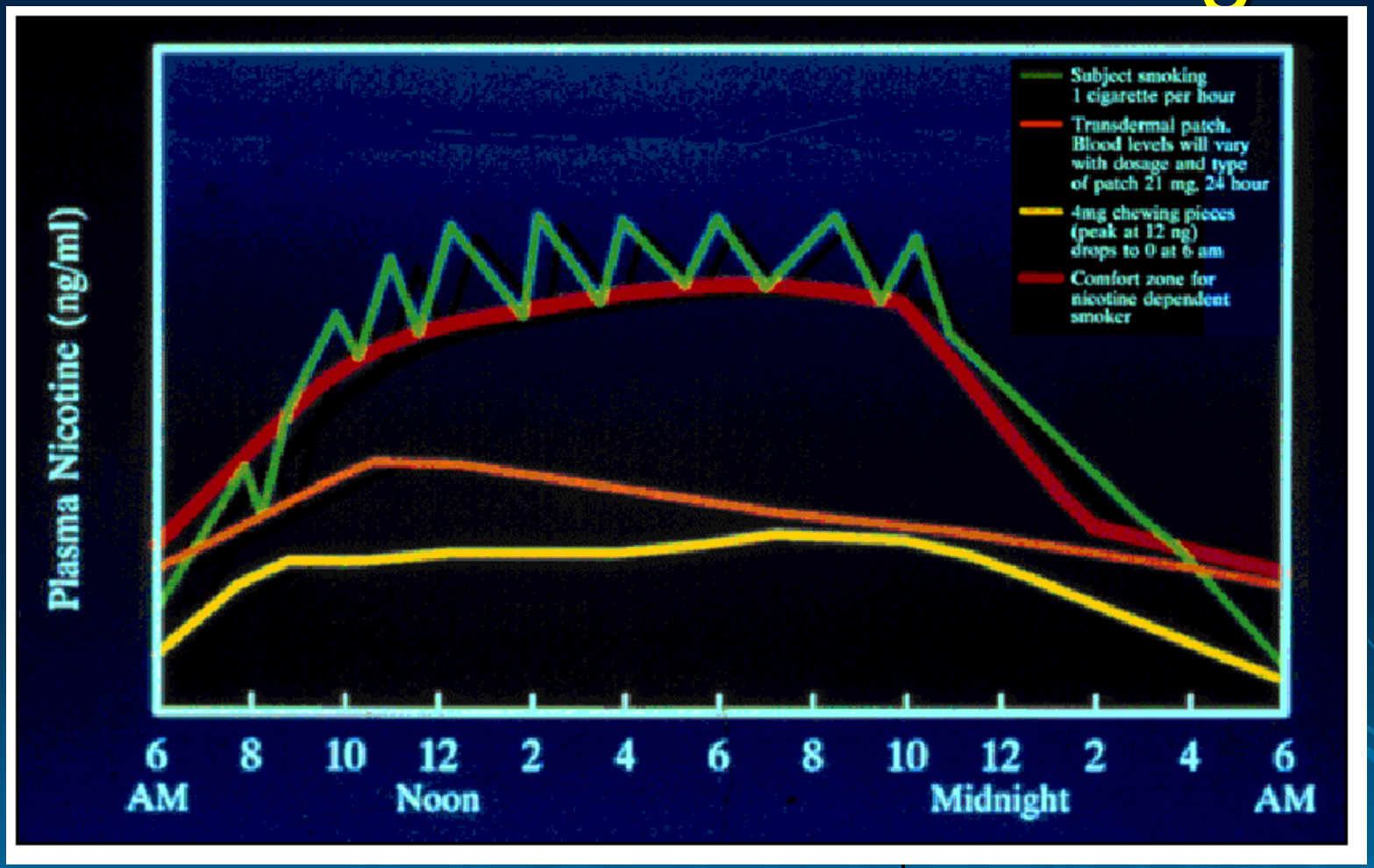
Nicotine replacement therapy (NRT)

- **Long acting: Patch**
- **Short acting:**
  - **Gum; Inhaler ; Lozenge ; Spray**

Bupropion SR (ZYBAN)

Varenicline (CHAMPIX)

Pharmacological interventions
Nicotine levels: the first target



Nicotine Replacement Therapy

- Patches
- 24 hour continuous dose of nicotine
- 21, 14 and 7mg patches

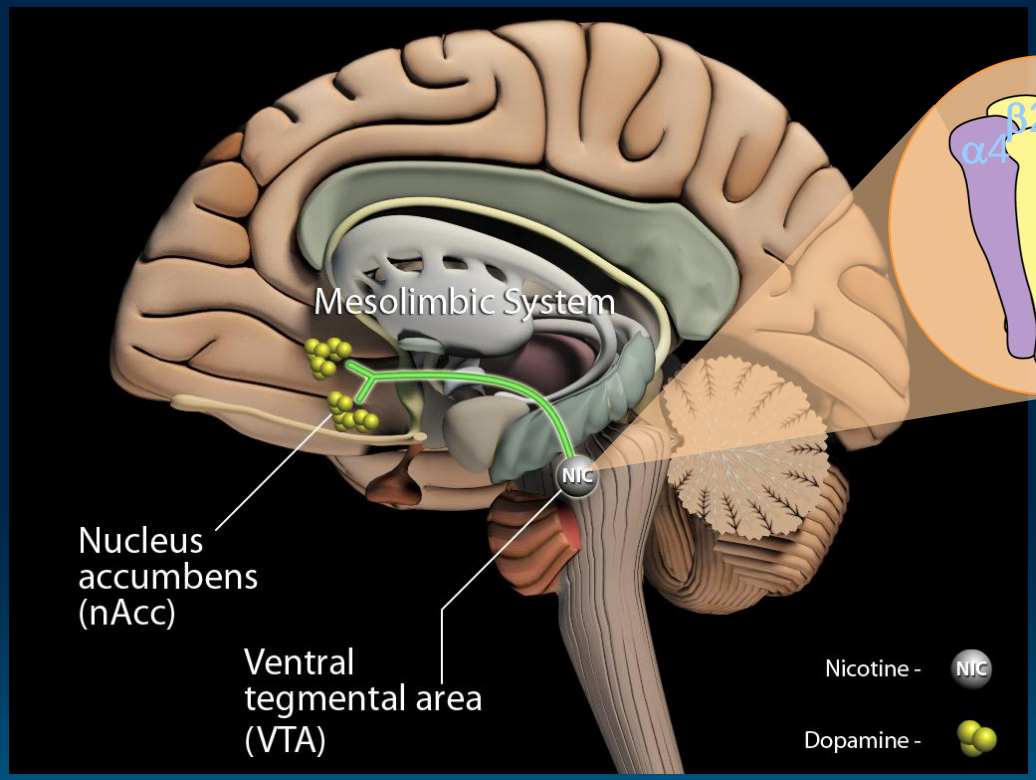
- Gums
- 2 & 4 mg doses
- Oral Gratification

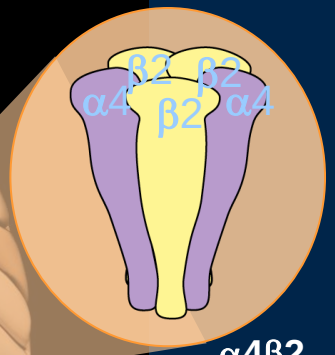
- Inhaler
- 10 mg of nicotine
- /cartridge
- Behavioral aspects

Zyban (Bupropion)

- **Originally designed to treat depression**
- **Shown to double ones chances of quitting**
- **Contraindications**
  - Seizure History
  - Eating Disorder
  - MAOI Medications
  - Using Bupropion, sensitivity to Bupropion

Varenicline a partial agonist toward the α4β2 nicotinic acetylcholine receptor





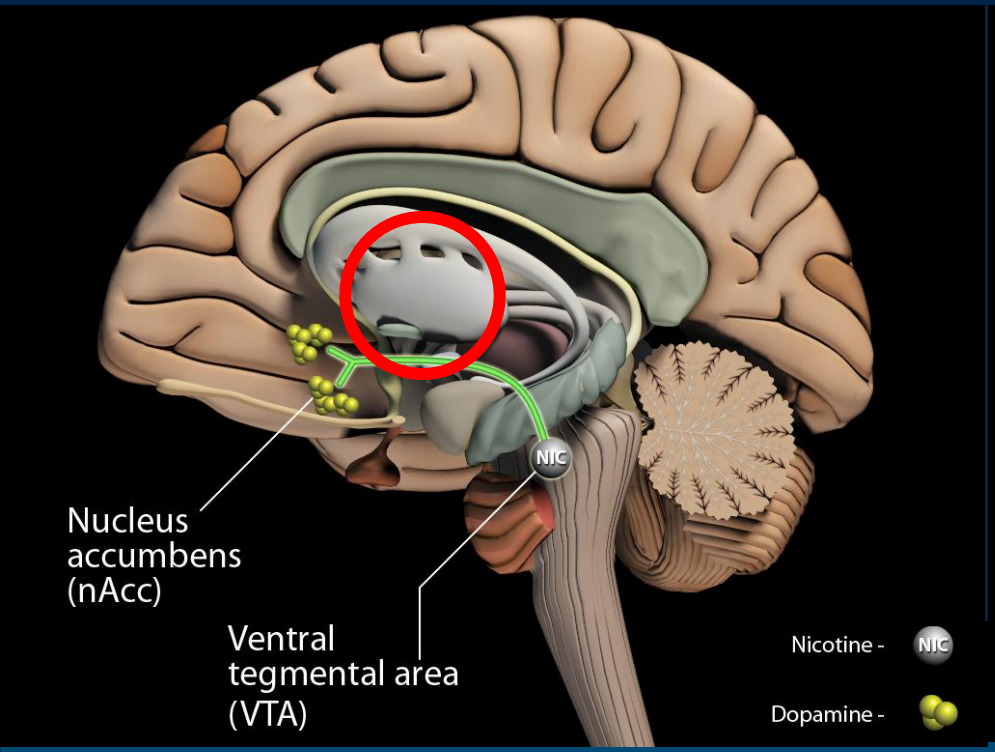
α4β2 Nicotinic Receptor

- Nicotine binds preferentially to nicotinic acetylcholine (nACh) receptors in the central nervous system; one of them is the α4β2 nACh receptor in the Ventral Tegmental Area (VTA)
- After nicotine binds to the α4β2 nACh receptor in the VTA, it results in a release of dopamine in the Nucleus Accumbens (nAcc), which is believed to be linked to reward

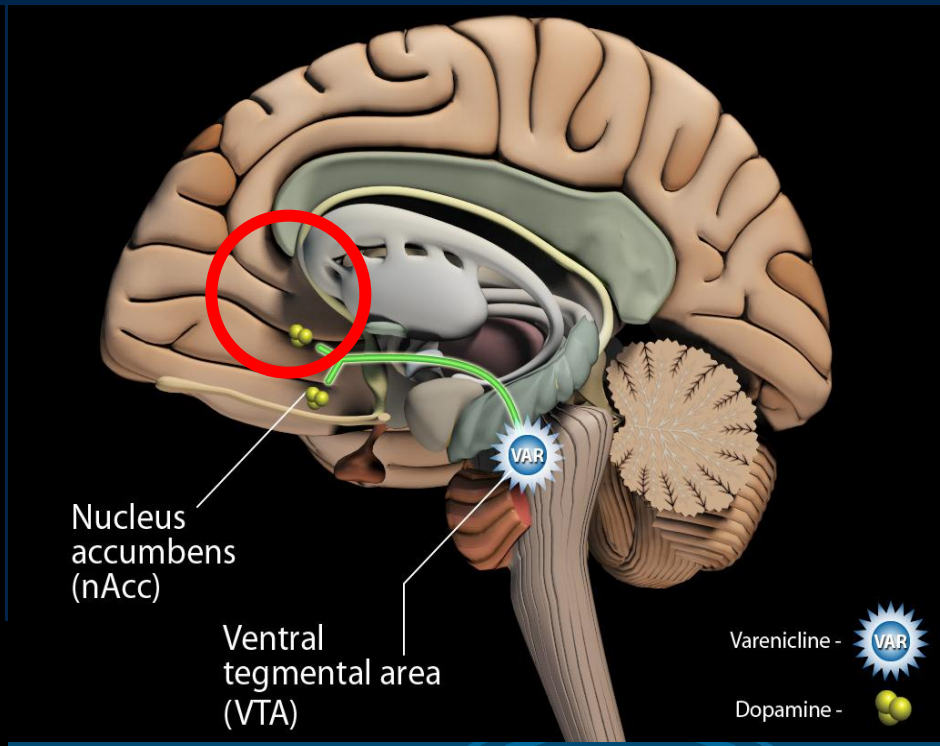
Foulds J. *Int J Clin Pract* 2006;60:571-576

Varenicline a partial agonist toward the α4β2 nicotinic acetylcholine receptor

Nicotine

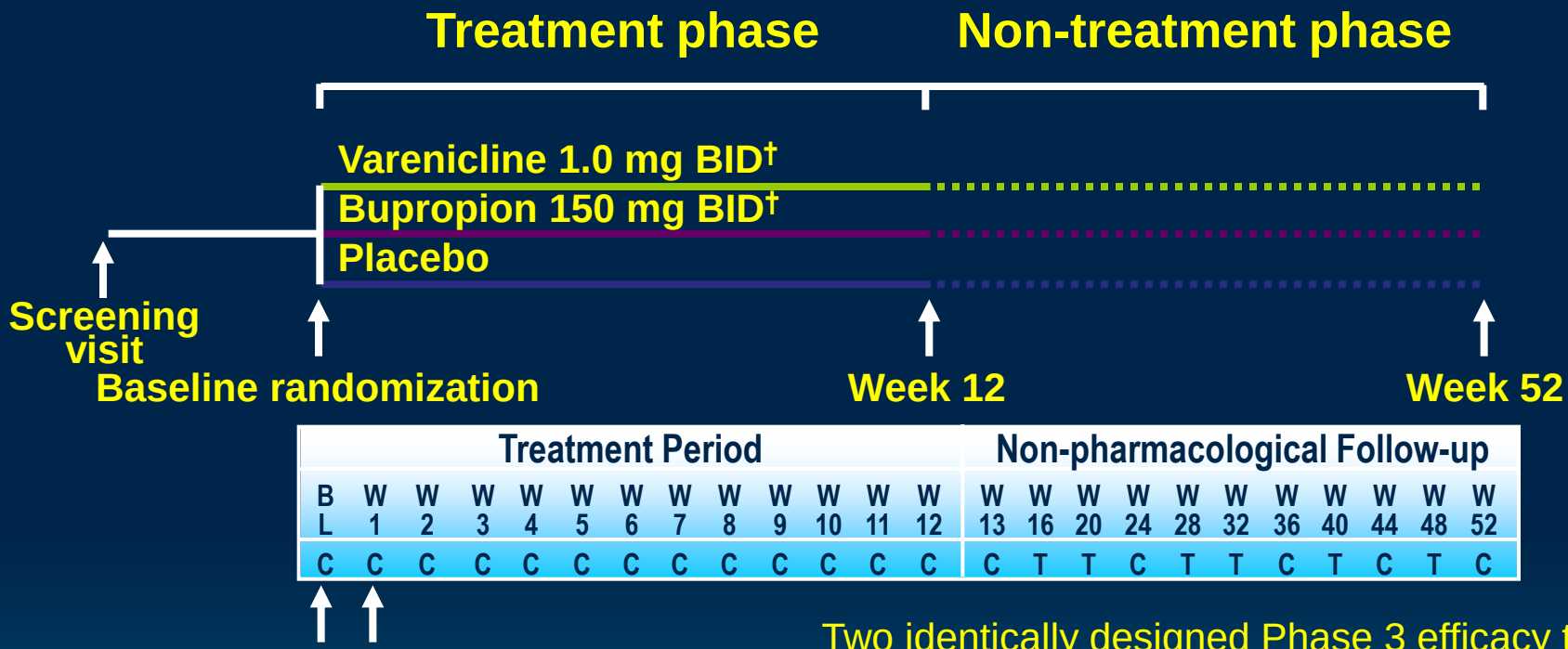


Varenicline



1. Foulds J. *Int J Clin Pract* 2006;60:571-576.
2. CHAMPIX Product Monograph, Pfizer Canada Inc., January 2007.
3. Coe JW *et al. J Med Chem* 2005;48:3474-3477

Varenicline Comparative Studies Design[1,2]



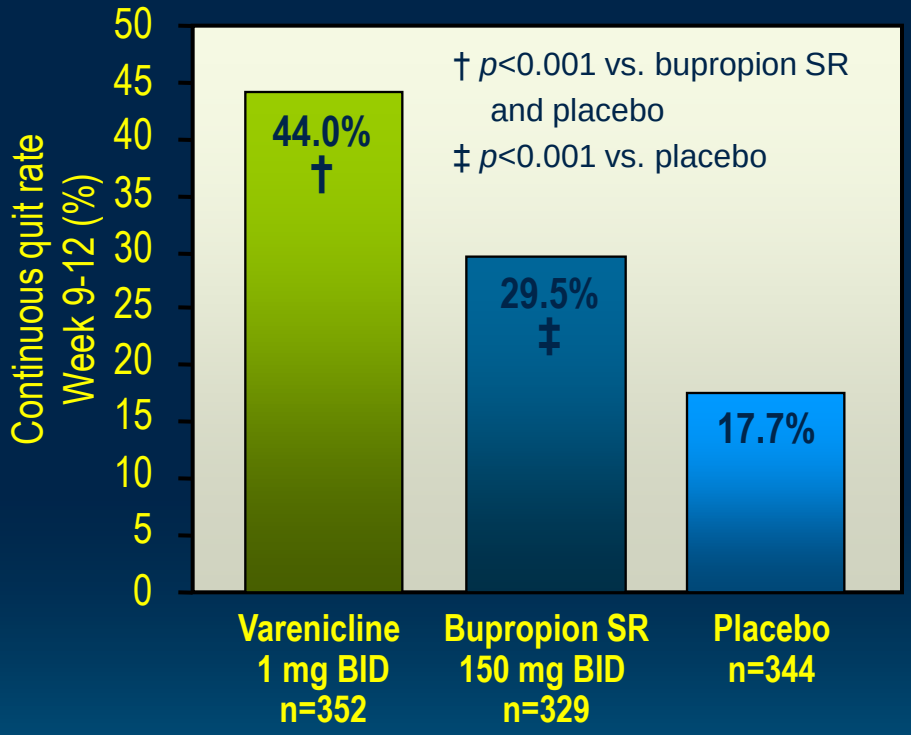
†Titrated during Week 1.
BL = Baseline; W = Week;
C = Clinic visit; T = Telephone contact

Two identically designed Phase 3 efficacy trials
Varenicline 1.0 mg BID vs. placebo or bupropion SR 150 mg BID
12 weeks of active treatment followed by 40 weeks of non-pharmacologic follow-up

1. Gonzales D *et al. JAMA* 2006;296:47-55.
2. Jorenby DE *et al. JAMA* 2006;296:56-63.

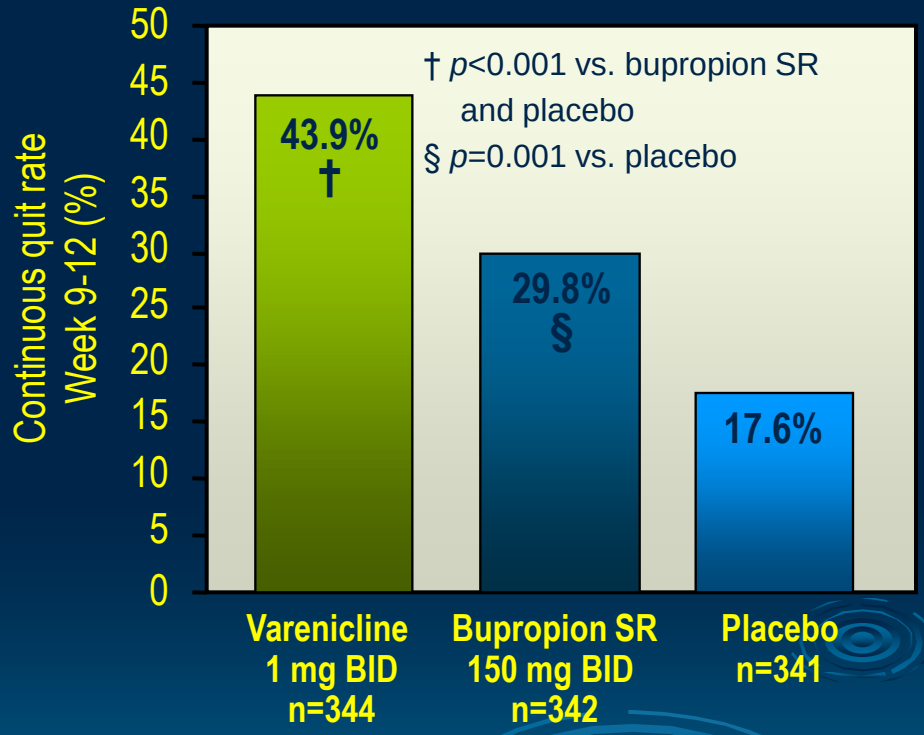
Varenicline Comparative Studies 4-Week Continuous Quit Rates Weeks 9-12[1,2]

Study 1: Gonzales *et al.*[1]



Odds ratio	
varenicline vs. placebo:	3.85; *p*<0.001
varenicline vs. bupropion SR:	1.93; *p*<0.001

Study 2: Jorenby *et al.*[2]

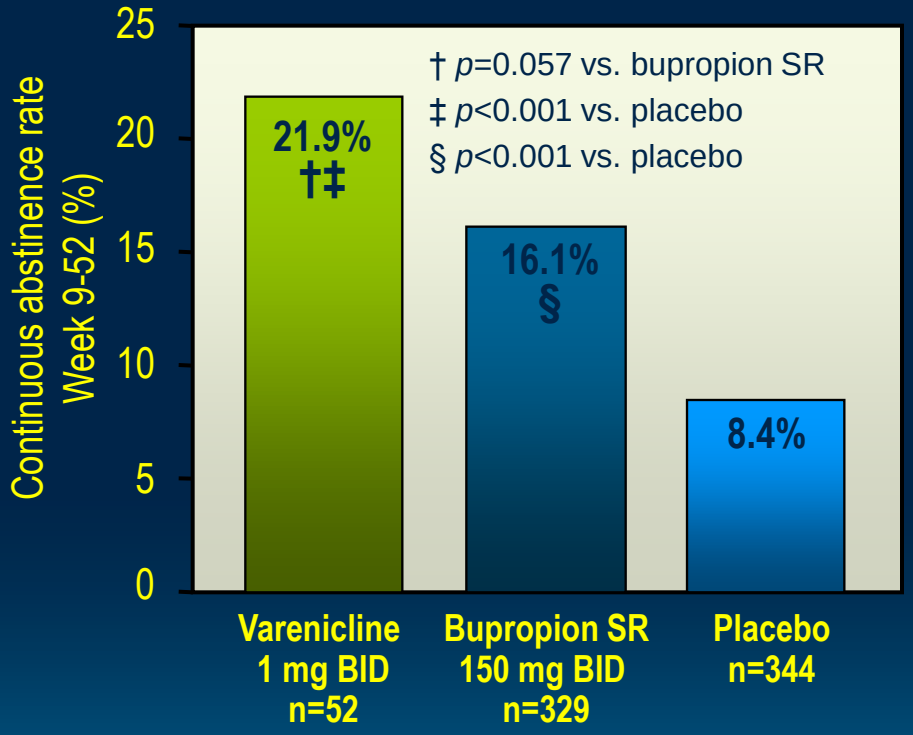


Odds ratio	
varenicline vs. placebo:	3.85; *p*<0.001
varenicline vs. bupropion SR:	1.90; *p*<0.001

1. Gonzales D *et al. JAMA* 2006;296:47-55.
2. Jorenby DE *et al. JAMA* 2006;296:56-63.

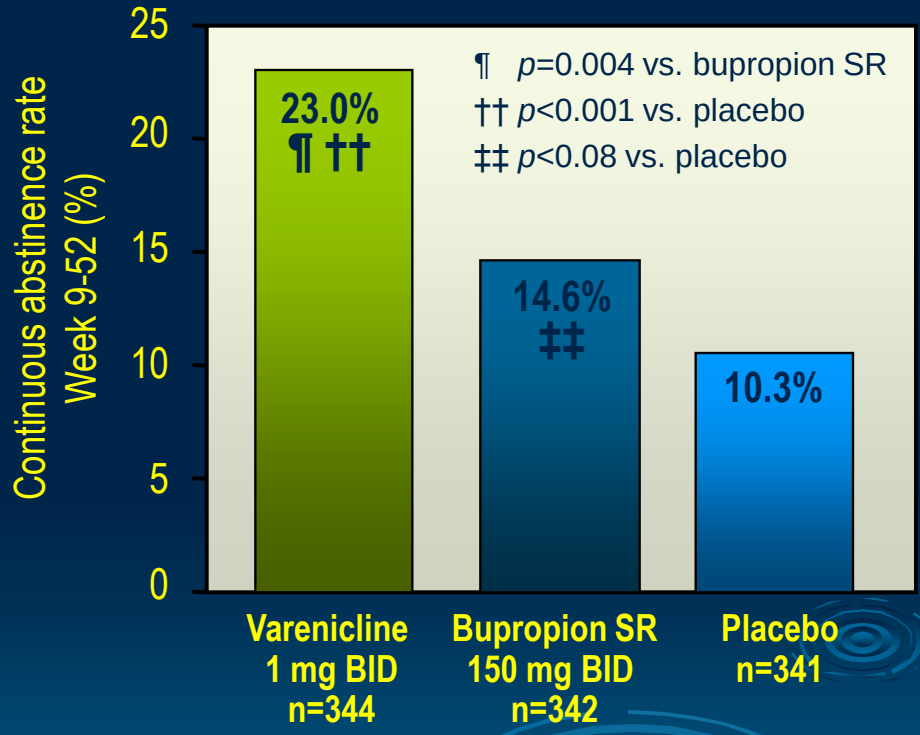
Varenicline Comparative Studies Continuous Abstinence Rates Weeks 9-52[1,2]

Study 1: Gonzales *et al.*[1]



Odds ratio
varenicline vs. placebo: 3.09; $p<0.001$
varenicline vs. bupropion SR: 1.46; $p=0.057$

Study 2: Jorenby *et al.*[2]



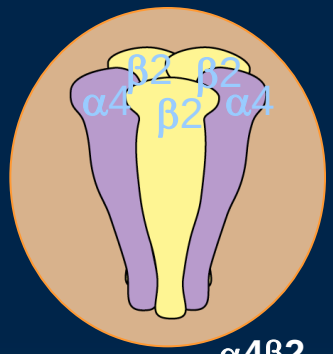
Odds ratio
varenicline vs. placebo: 2.66; $p<0.001$
varenicline vs. bupropion SR: 1.77; $p=0.004$

1. Gonzales D *et al. JAMA* 2006;296:47-55.
2. Jorenby DE *et al. JAMA* 2006;296:56-63.

Better treatments are needed

- ONE OVER TWO SMOKERS WILL DIE FROM TOBACCO RELATED ILLNESS
- Despite treatment, majority of smokers relapse
- Better treatment are required

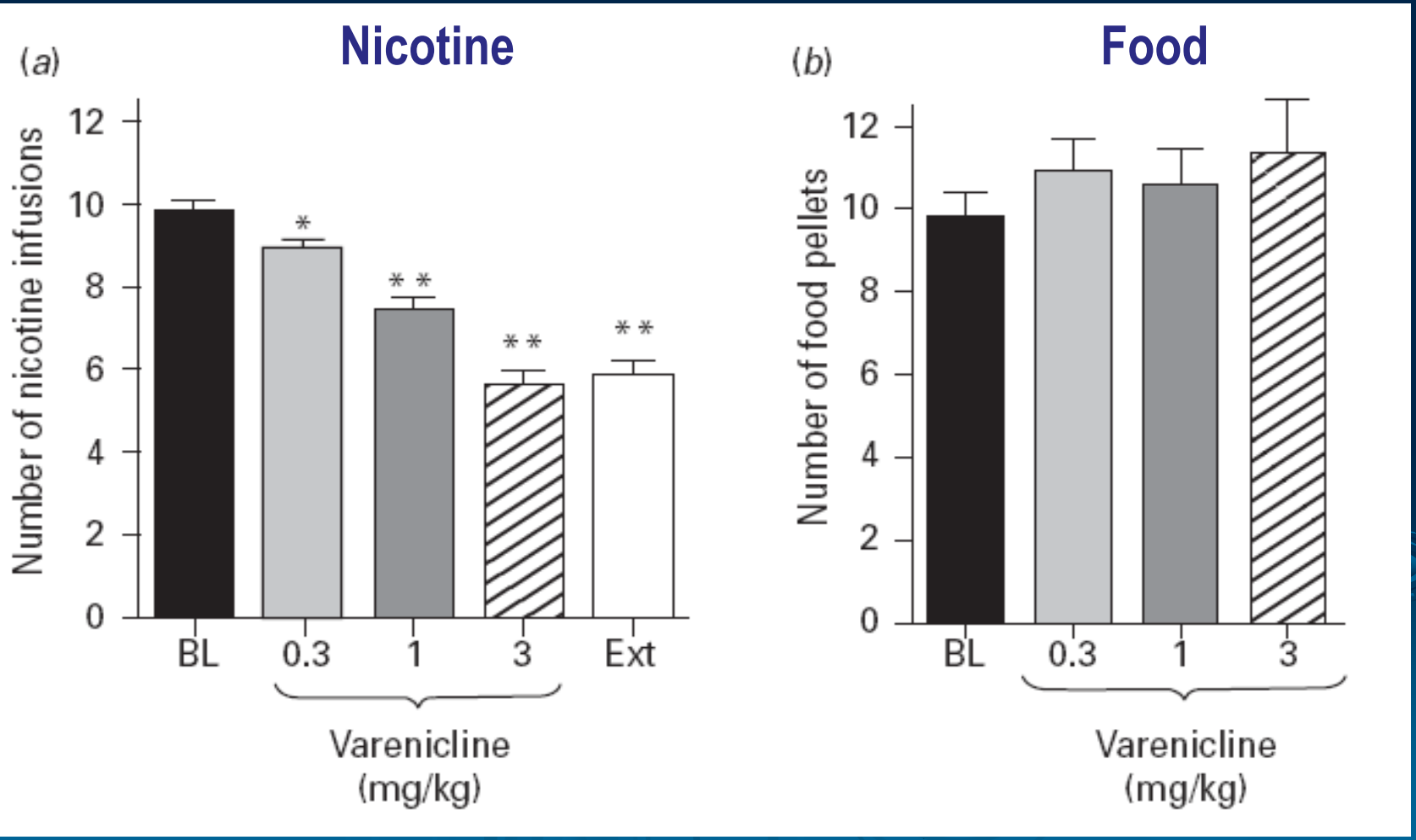
Using animal models to screen for potential novel medications



α4β2 Nicotinic Receptor

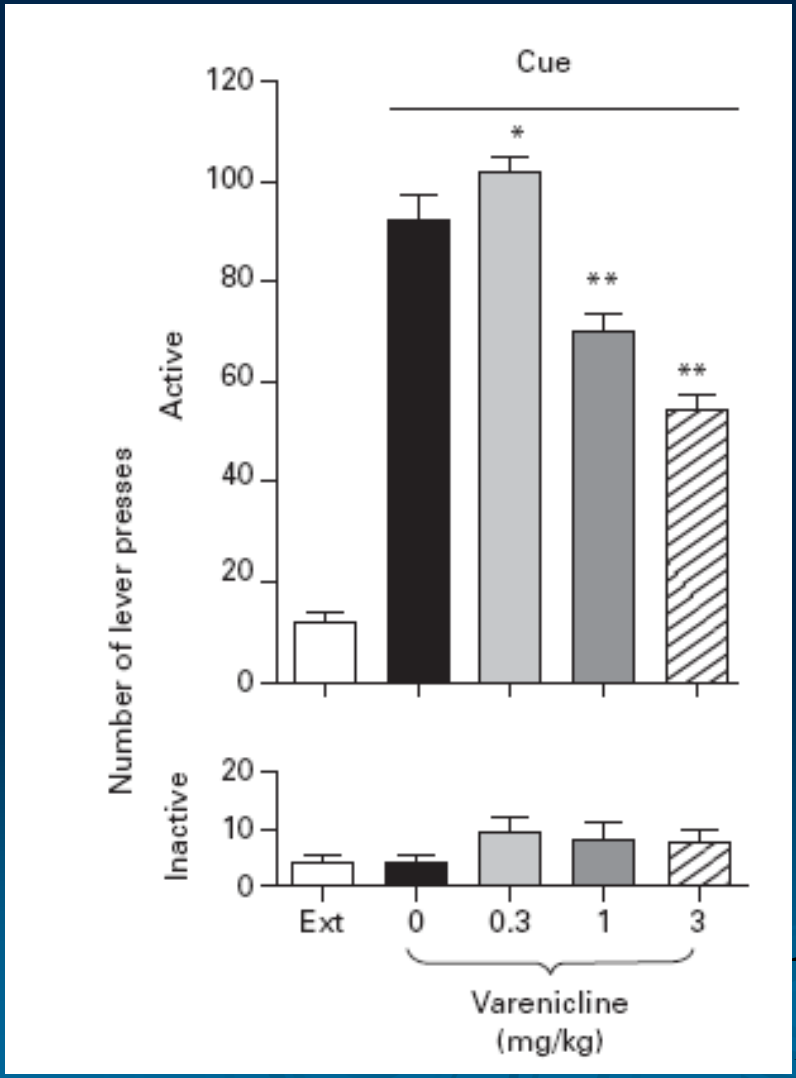
- Impact of Varenicline on animal models
- Two potential new strategies: cannabinoid system and insular cortex

Varenicline decreases motivation for nicotine in rats



Le Foll et al, 2011

Effects of varenicline on reinstatement of nicotine seeking



- Experimental approach #1

CANNABINOID SYSTEM

The endogenous cannabinoid system and its receptors

- **CB_1 receptors** are localized mainly in the central nervous system (**CNS)** and are thought to mediate most central effects of THC and its synthetic analogs and their liability for abuse

- **CB_2** receptors are primarily localized in peripheral organs and are involved in modulation of immune functions, but have been recently identified in the CNS and proposed to play a role in drug addiction

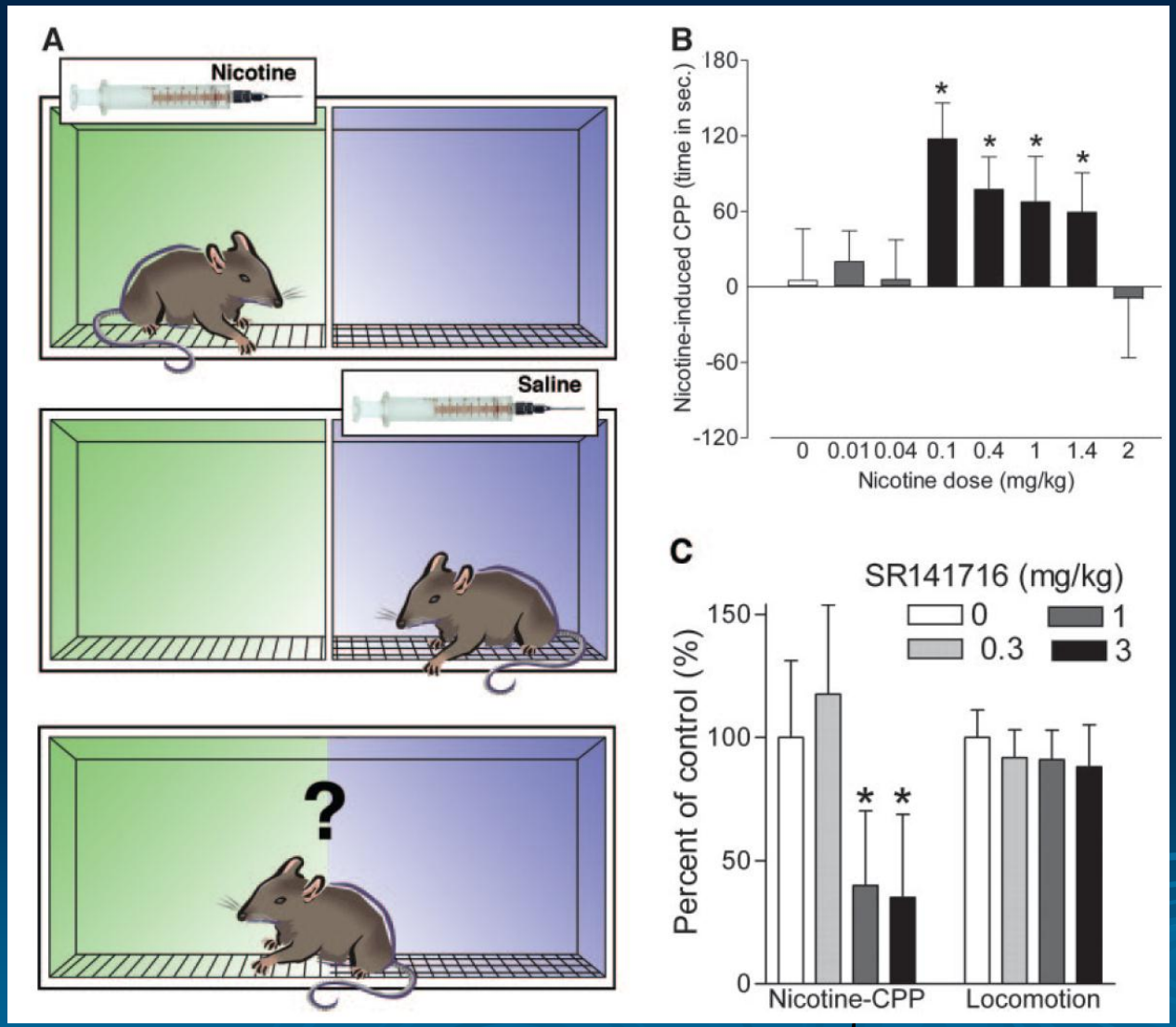
- Two endogenous cannabinoid (anandamide and 2 AG).

- Degradation system: FAAH enzyme for anandamide and MAGL for 2 AG.

- Reuptake transport system for anandamide. Pharmaceutical drugs under development AM 404 and VDM11 that elevate anandamide levels in the brain

Effect of blocking the system

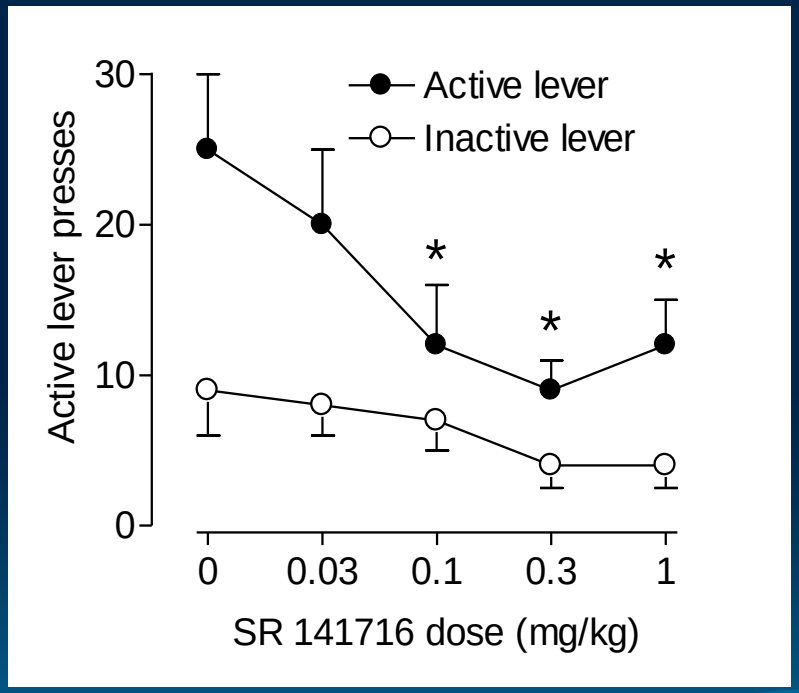
Rimonabant (SR 141716) a CB1 antagonist blocks nicotine-induced conditioned place preferences



From Le Foll *et al., 2005*

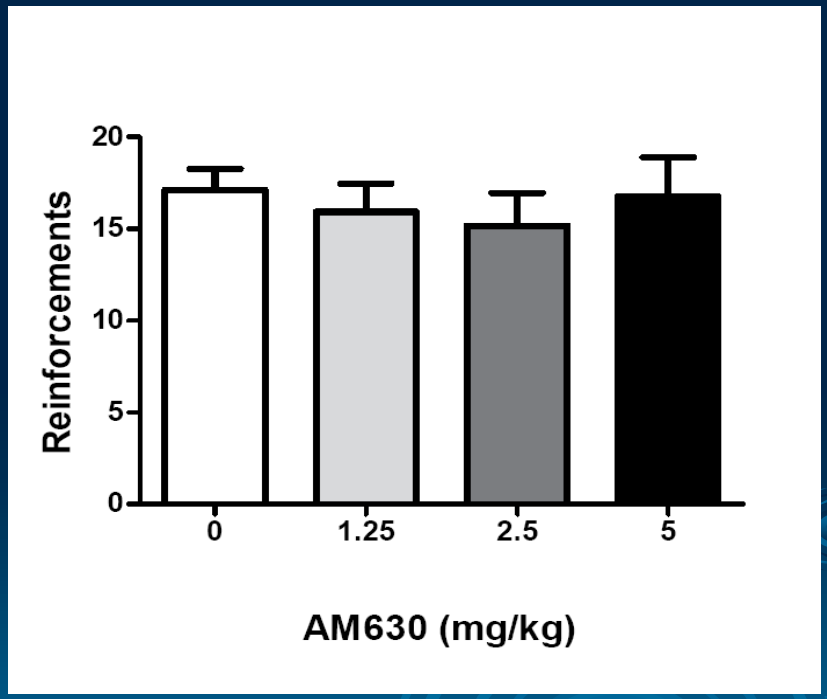
CB_1, but not CB_2, blockade decreases self-administration of nicotine under FR schedule

CB_1 blockade



Cohen *et al., 2002*

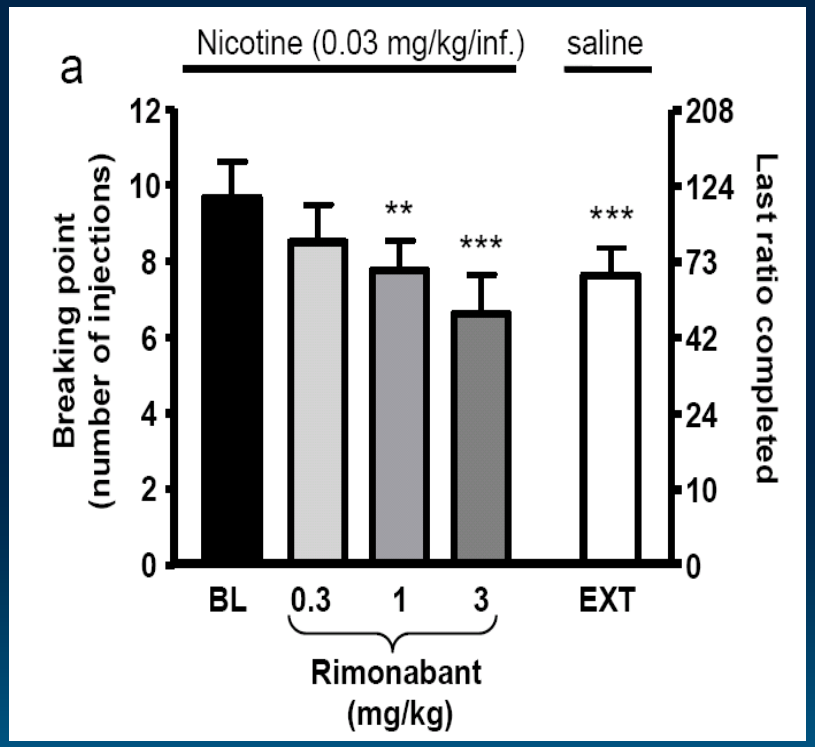
CB_2 blockade



Gamaleddin *et al., 2012*

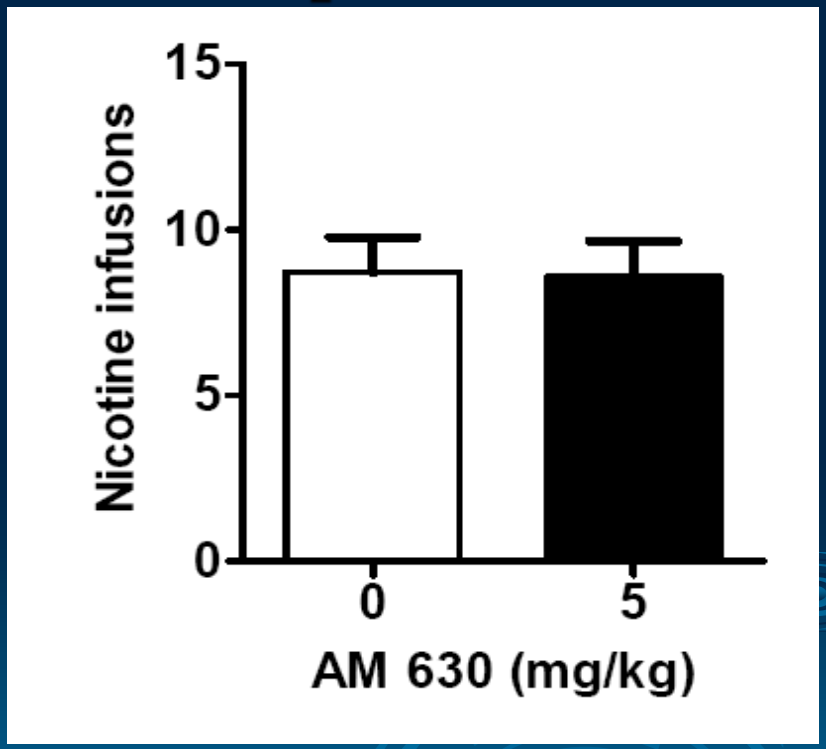
CB_1, but not CB_2, blockade decreases motivation for nicotine under PR schedule

CB_1 blockade



Forget *et al., 2009*

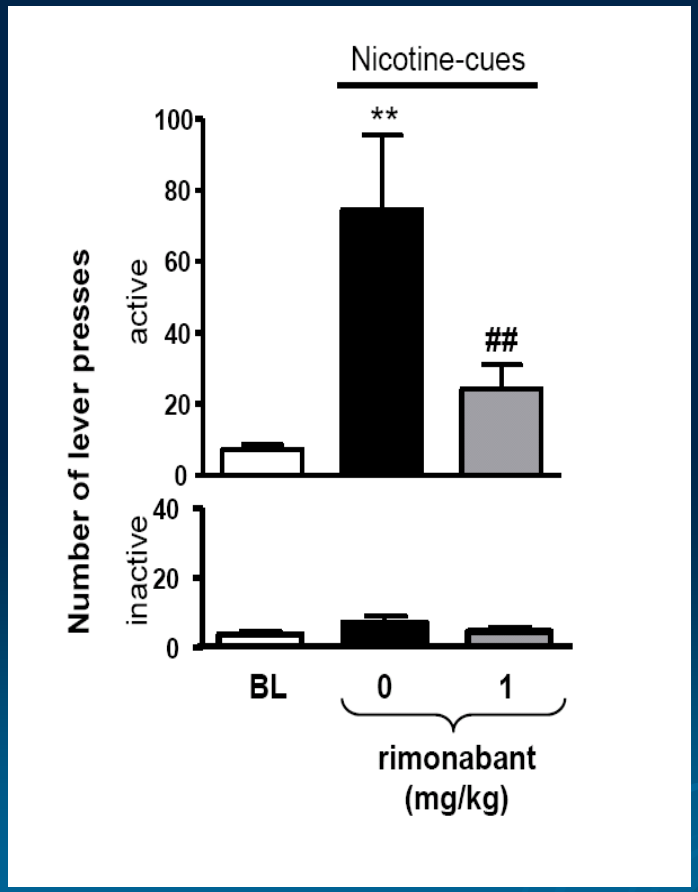
CB_2 blockade



Gamaleddin *et al., 2012*

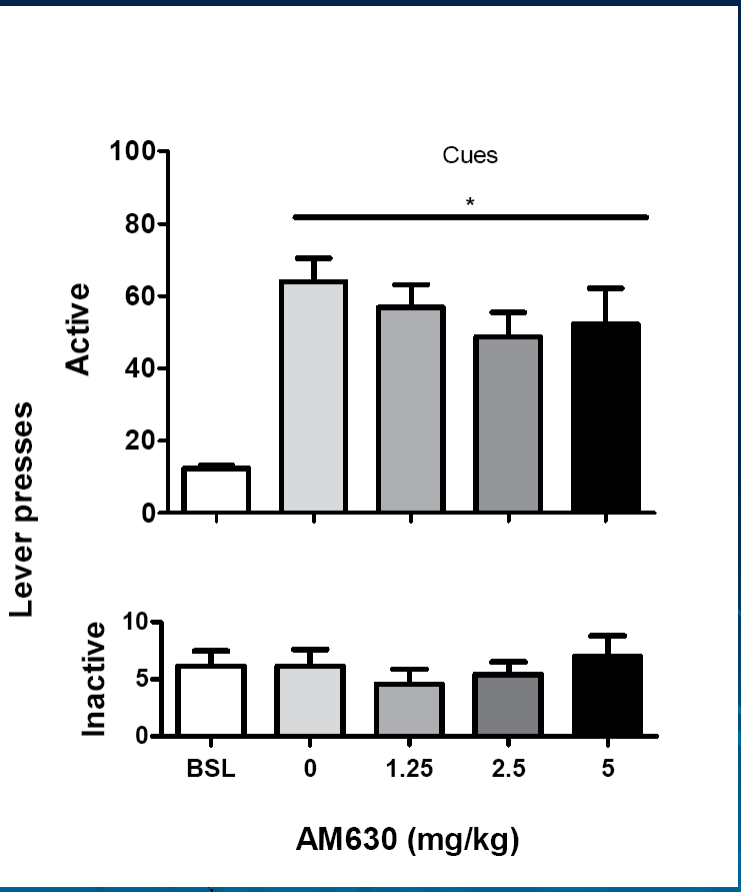
CB_1, but not CB_2, blockade attenuates reinstatement of nicotine seeking induced by cues

CB_1 blockade



Forget *et al., 2009*

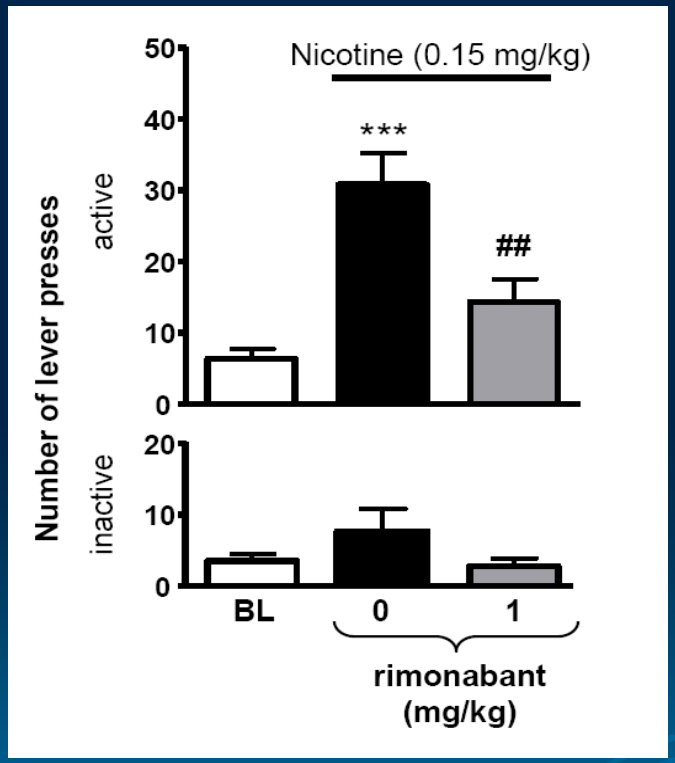
CB_2 blockade



Gamaleddin *et al., 2012*

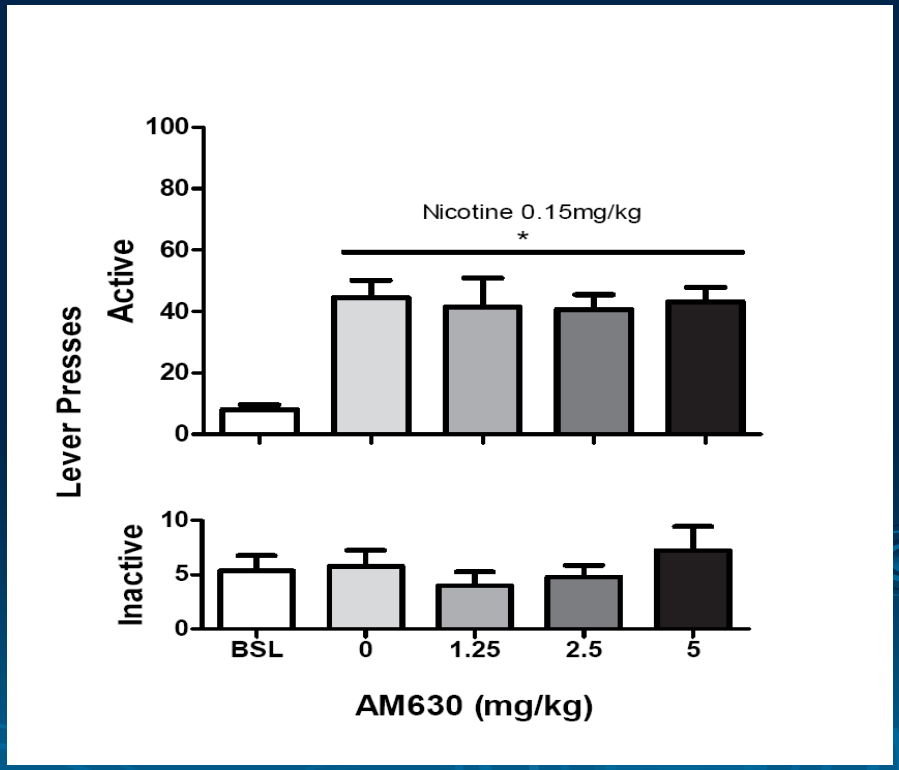
Rimonabant decreases reinstatement of nicotine-seeking induced by nicotine priming

CB_1 blockade



Forget *et al., 2009*

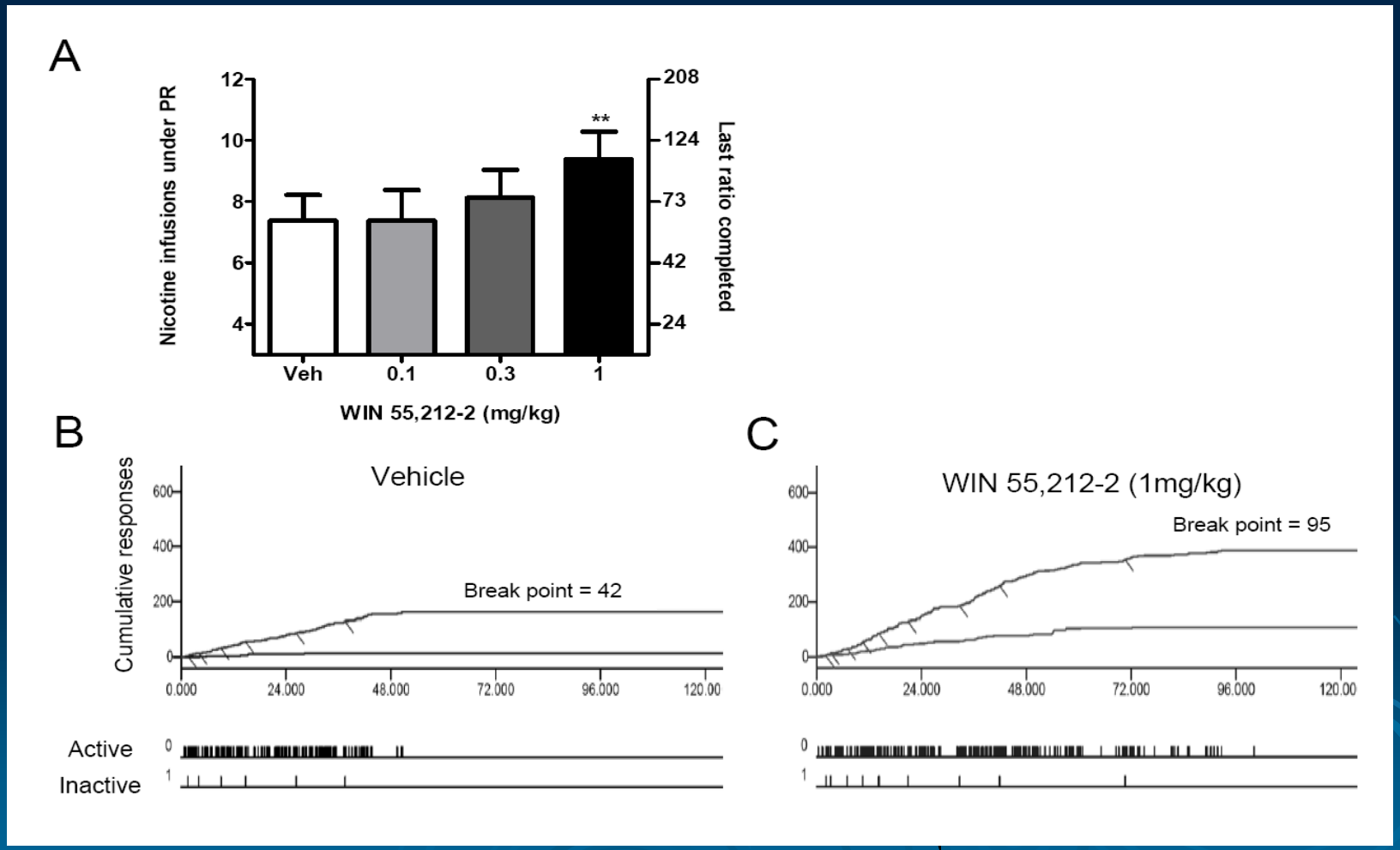
CB_2 blockade



Gamaleddin *et al.*, *2012*

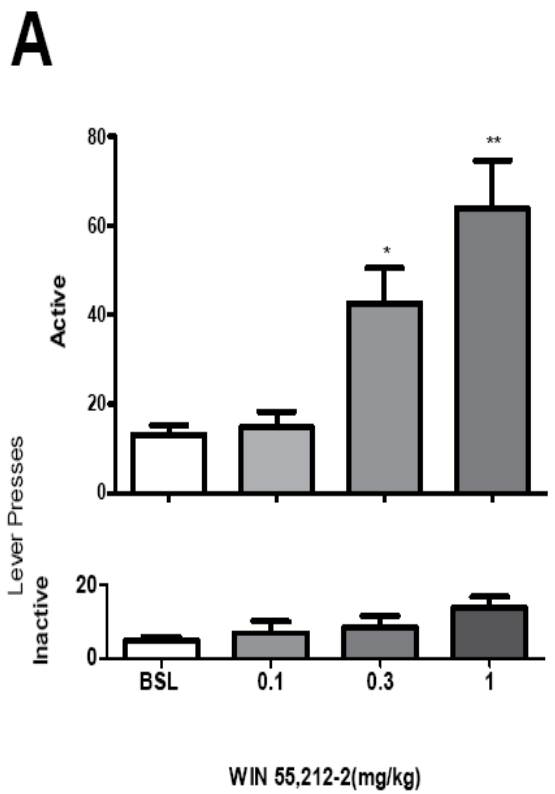
Effect of stimulating the system

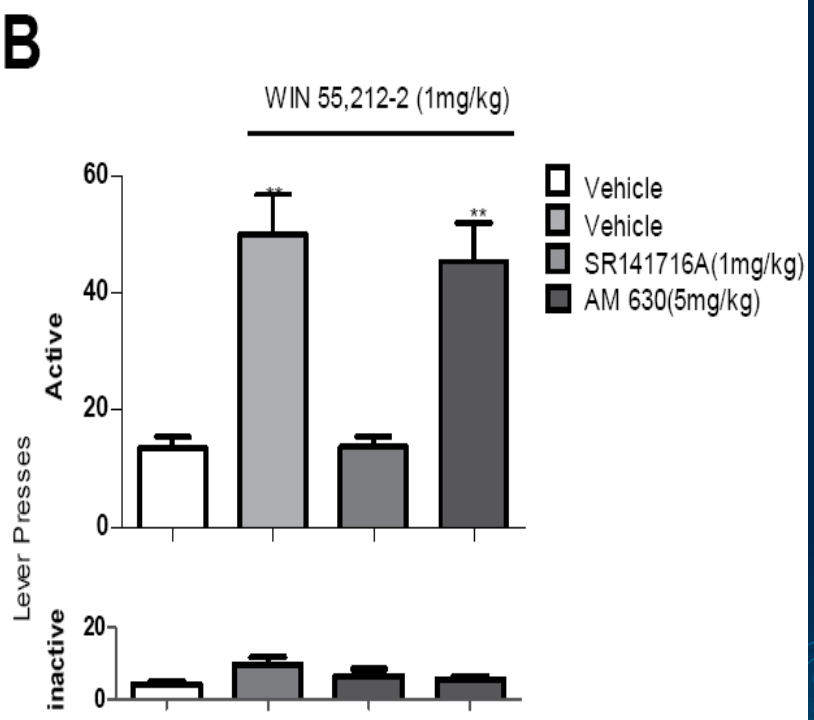
Effect of WIN 55,212-2 on nicotine self administration under PR schedule of reinforcement



Gamaleddin et al., 2012

A CB1/CB2 agonist (WIN 55,212-2) precipitates reinstatement of nicotine-seeking





Gamaleddin et al., 2012

The rise and fall of Rimonabant as a medication for obesity and metabolic risk factors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Rimonabant on Metabolic Risk Factors in Overweight Patients with Dyslipidemia

Jean-Pierre Després, Ph.D., Alain Golay, M.D., and Lars Sjöström, M.D., Ph.D., for the Rimonabant in Obesity–Lipids Study Group*

N ENGL J MED 353;20 WWW.NEJM.ORG NOVEMBER 17, 2005

Effect of Rimonabant, a Cannabinoid-1 Receptor Blocker, on Weight and Cardiometabolic Risk Factors in Overweight or Obese Patients

RIO-North America: A Randomized Controlled Trial

JAMA. 2006;295:761-775

Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study

*Luc F Van Gaal, Aila M Rissanen, André J Scheen, Olivier Ziegler, Stephan Rössner, for the RIO-Europe Study Group**

Lancet 2005; 365: 1389–97

STRATUS Program in Smoking Cessation

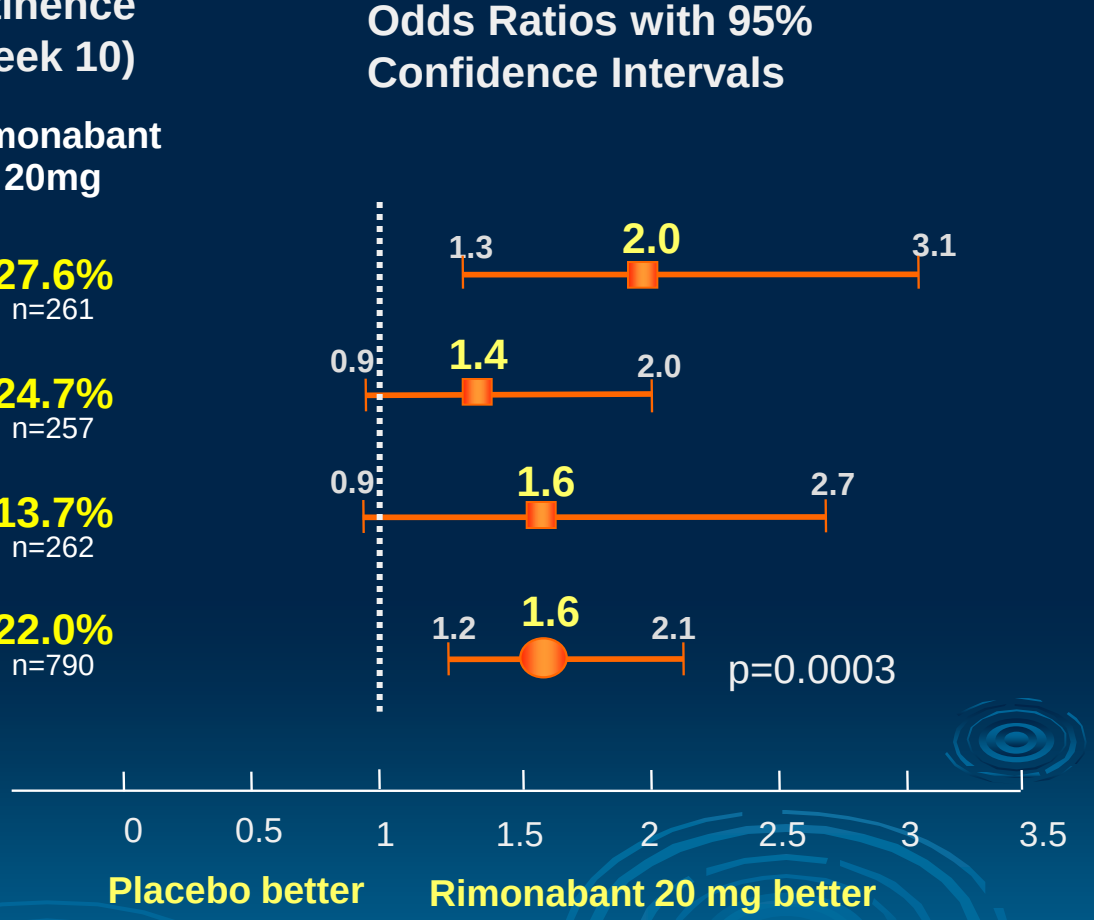
- Total of >7000 patients enrolled
- Consistent with RIO program, utilized rimonabant at dosages of 20 mg and 5 mg* daily
- Four phase 3 studies completed
  - STRATUS-US: 10-week treatment, 42-week f-u
  - STRATUS-Europe: 10-week treatment , 42-week f-u
  - STRATUS-Meta*: 10-week treatment
  - STRATUS-Worldwide: 1-year treatment, 1-year f-u

*only 20 mg dose evaluated in STRATUS-Meta

Continuous Abstinence During Last 4 Weeks of Treatment

	Prolonged abstinence (Week 7 to Week 10)	
	Placebo	Rimonabant 20mg
STRATUS US	**16.1%** n=261	**27.6%** n=261
STRATUS EU	**19.6%** n=250	**24.7%** n=257
STRATUS META	**9.3%** n=268	**13.7%** n=262
Pool STRATUS US/EU/META	**15.0%** n=789	**22.0%** n=790

Heterogeneity: p=0.434



Cinciripini PM et al. Pooled analysis of three short-term, randomized, double-blind, placebo-controlled trials with rimonabant 20 mg/d in smoking cessation. Poster presented at the 8th Annual Conference of the SRNT Europe, Kusadasi, Turkey, September 2006.

Rimonabant has been withdrawn due to increased risk of psychiatric side effects

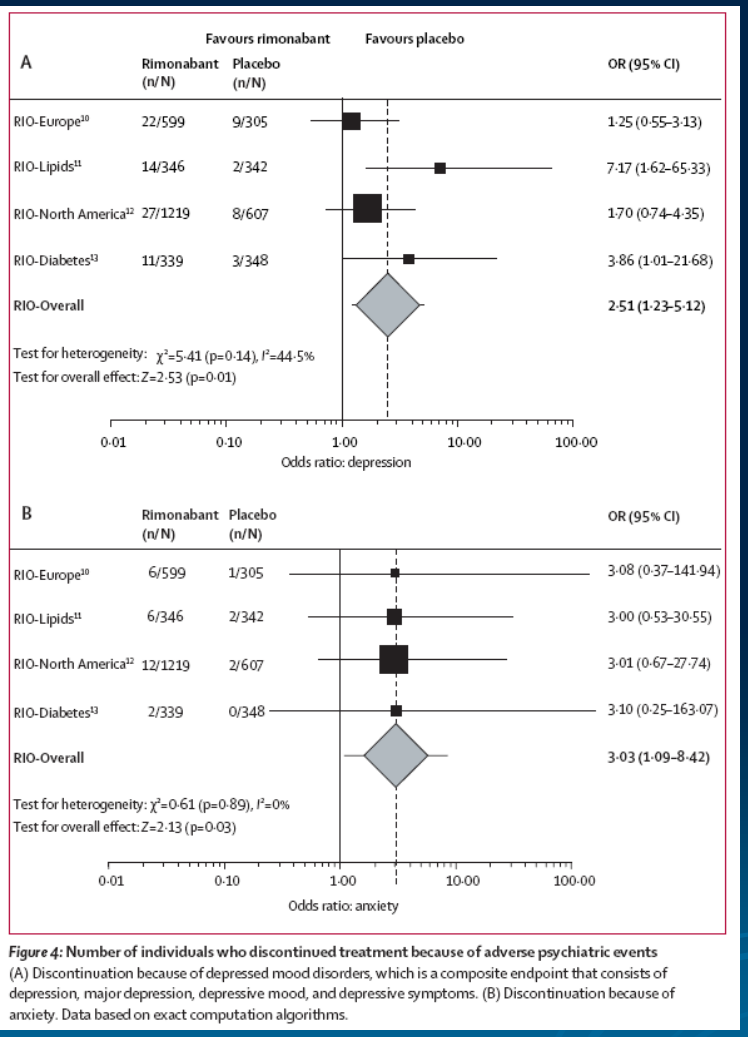


Figure 4: **Number of individuals who discontinued treatment because of adverse psychiatric events**
(A) Discontinuation because of depressed mood disorders, which is a composite endpoint that consists of depression, major depression, depressive mood, and depressive symptoms. (B) Discontinuation because of anxiety. Data based on exact computation algorithms.

Psychopharmacology
DOI 10.1007/s00213-009-1506-7

COMMENTARY

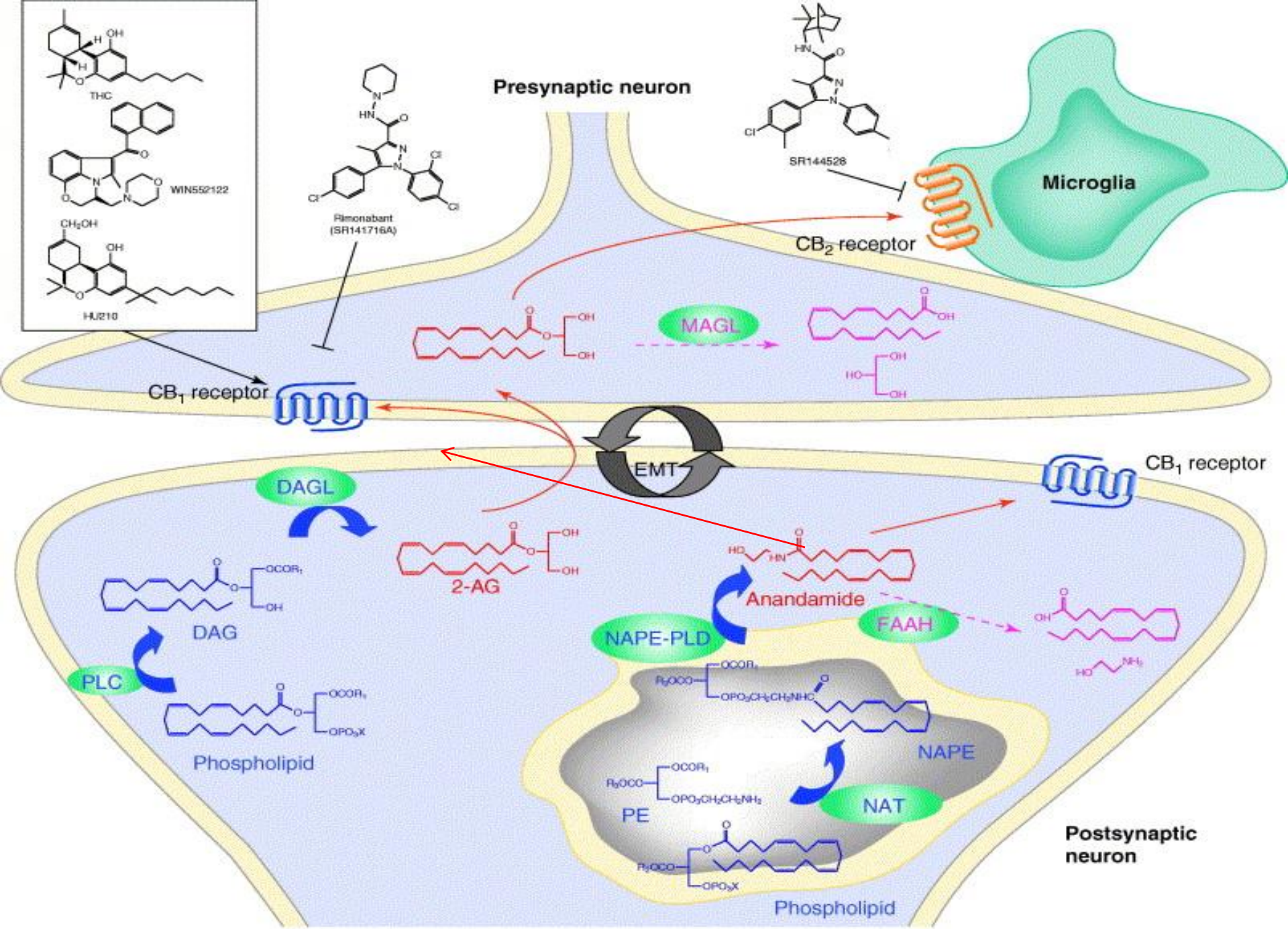
The future of endocannabinoid-oriented clinical research after CB_1 antagonists

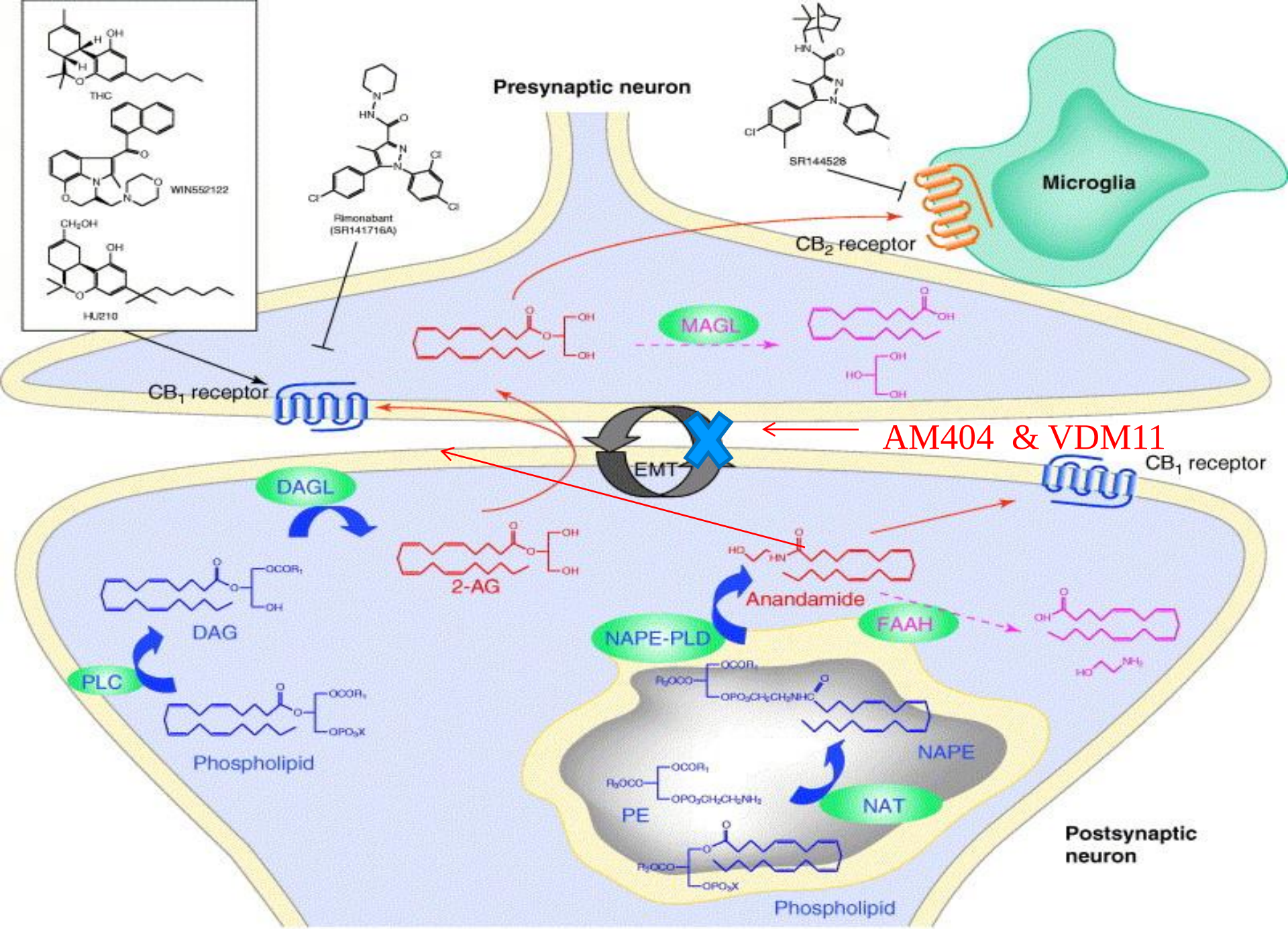
Bernard Le Foll · David A. Gorelick · Steven R. Goldberg

From Christensen et al. Lancet, 2007

Is the story over ?

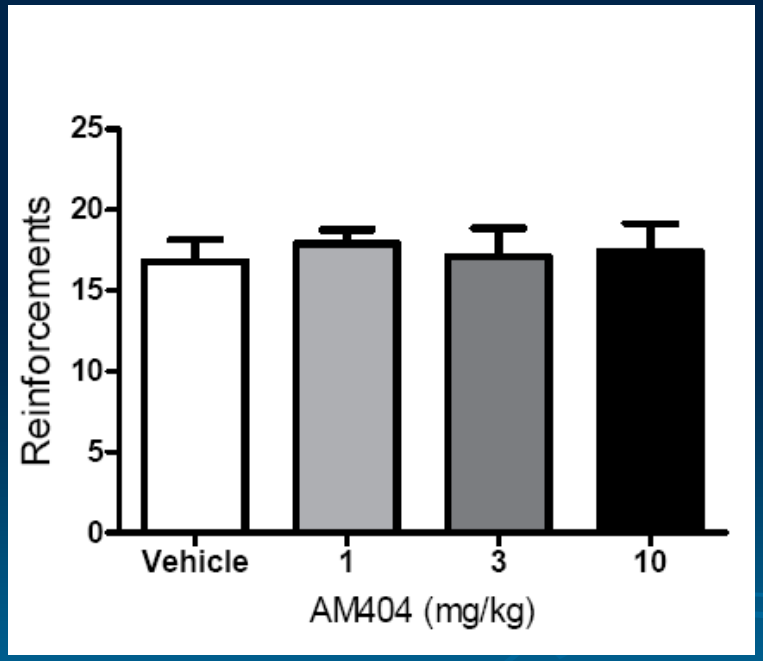
or can we modulate endogenous cannabinoid transmission differently to achieve good outcomes ?


THC
WIN552122
HU210
Rimonabant
(SR141716A)
SR144528
Presynaptic neuron
Microglia
CB2 receptor
MAGL
CB1 receptor
EMT
CB1 receptor
DAGL
2-AG
Anandamide
FAAH
DAG
NAPE-PLD
PLC
Phospholipid
NAPE
PE
NAT
Postsynaptic
neuron
Phospholipid


THC
WIN552122
HU210
Rimonabant
(SR141716A)
SR144528
Presynaptic neuron
Microglia
CB2 receptor
MAGL
CB1 receptor
EMT
AM404 & VDM11
CB1 receptor
DAGL
2-AG
DAG
PLC
Phospholipid
Anandamide
FAAH
NAPE-PLD
NAPE
NAT
PE
Phospholipid
Postsynaptic
neuron

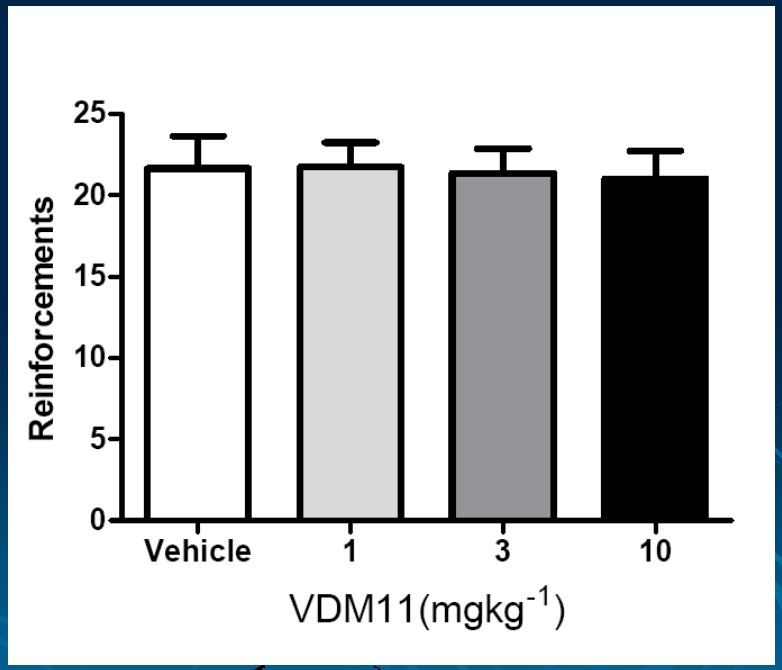
Effect of anandamide reuptake inhibitors AM404 & VDM11 on nicotine self-administration under Fixed ratio schedule of reinforcement

AM404



Gamaleddin *et al., under review*

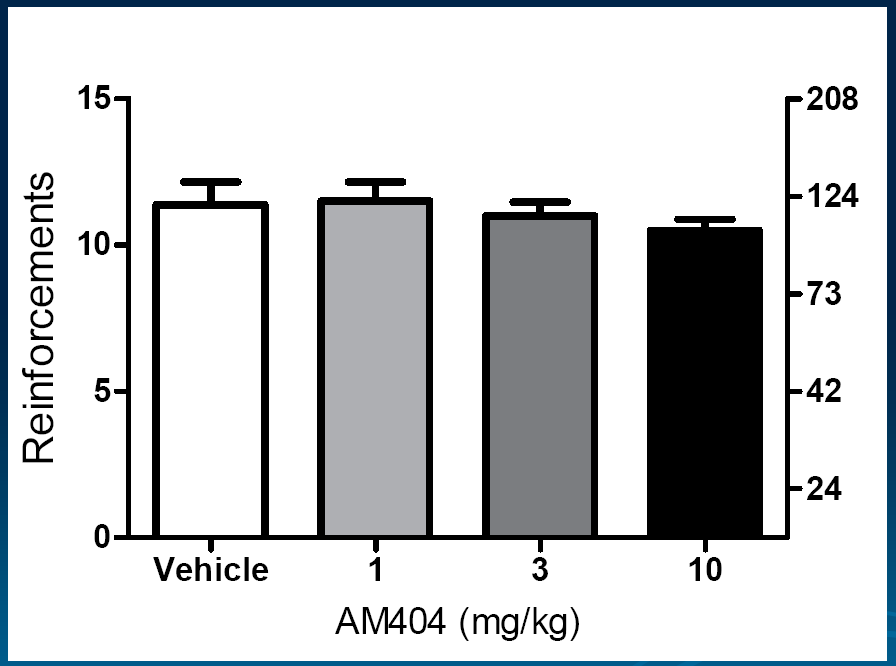
VDM11



Gamaleddin *et al., 2011b (BJP)*

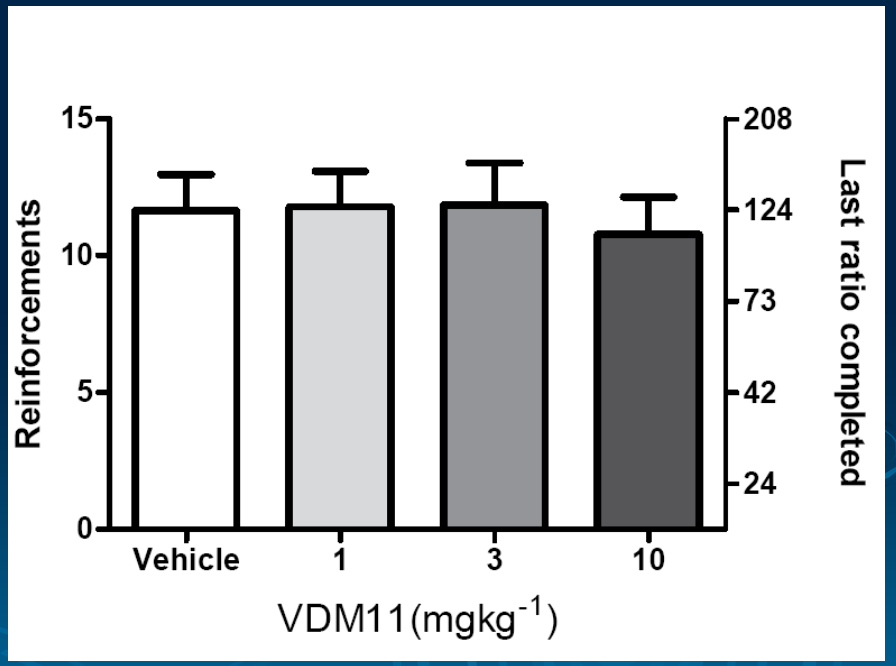
Effect of anandamide reuptake inhibitors AM404 and VDM11 on nicotine self administration under PR schedule

AM404



Gamaleddin *et al., under review*

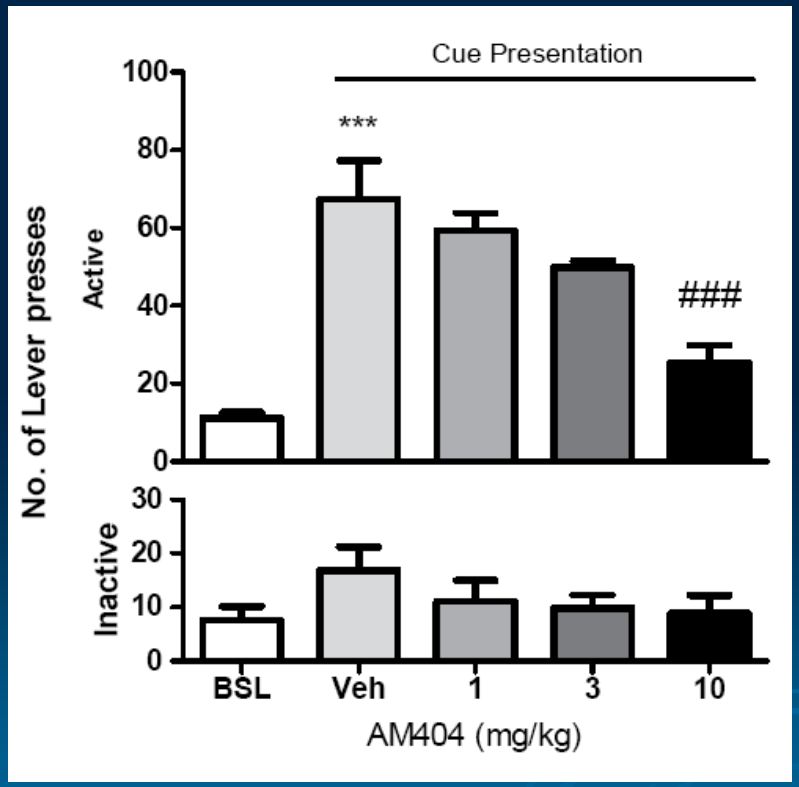
VDM11



Gamaleddin *et al., 2011b (BJP)*

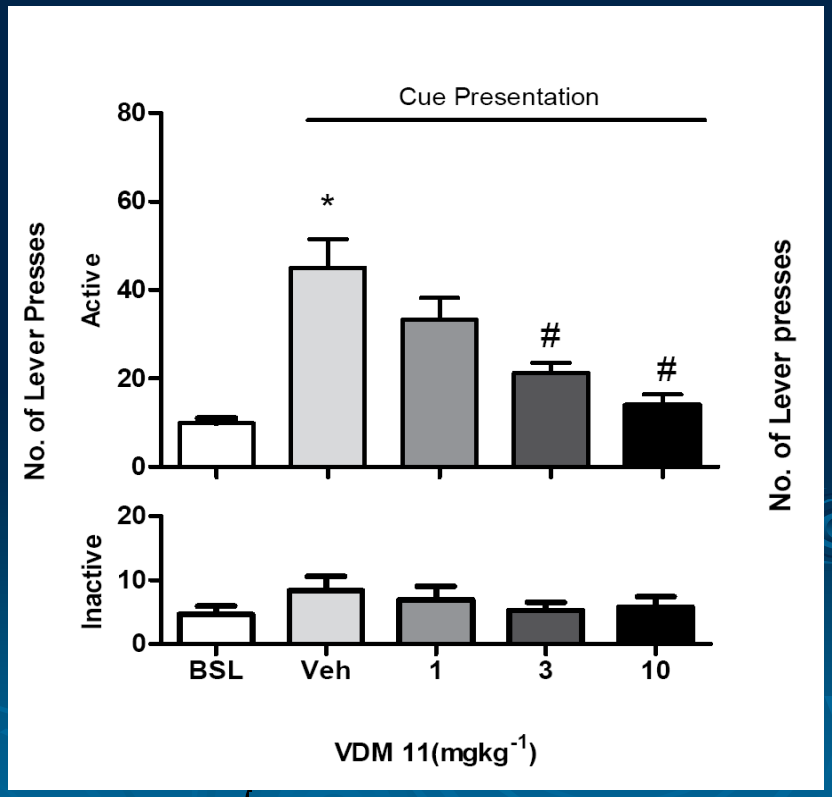
Effect of anandamide reuptake inhibitors AM404 and VDM11 on cue induced reinstatement of nicotine seeking

AM404



Gamaleddin *et al., under review*

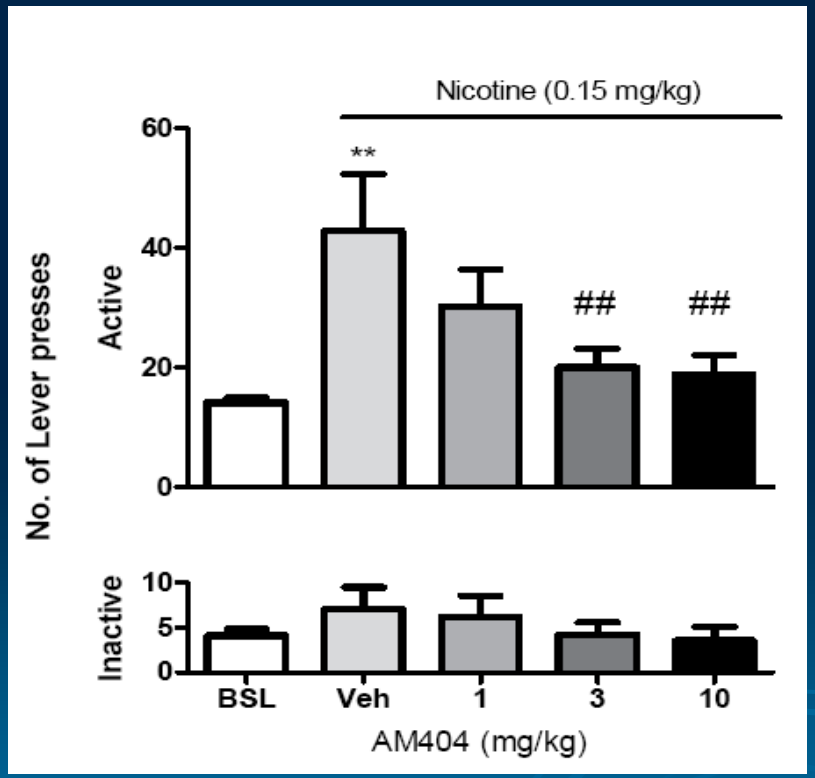
VDM11



Gamaleddin *et al., 2011b (BJP)*

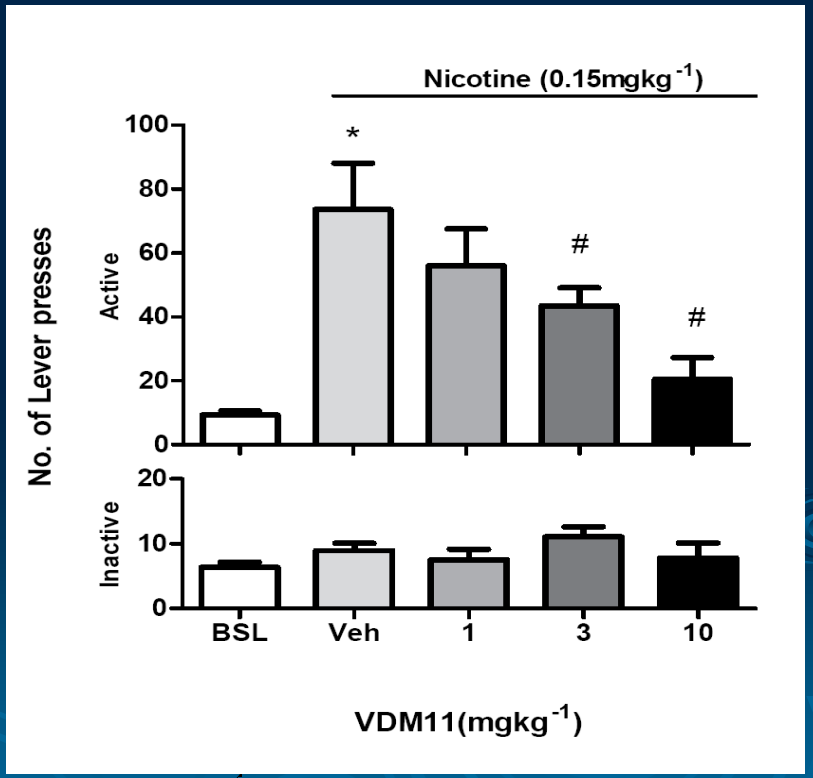
Effect of anandamide reuptake inhibitors AM404 and VDM11 on reinstatement of nicotine seeking induced by nicotine priming

AM404



Gamaleddin *et al*.,under review

VDM11



Gamaleddin *et al*.,2011b(BJP)

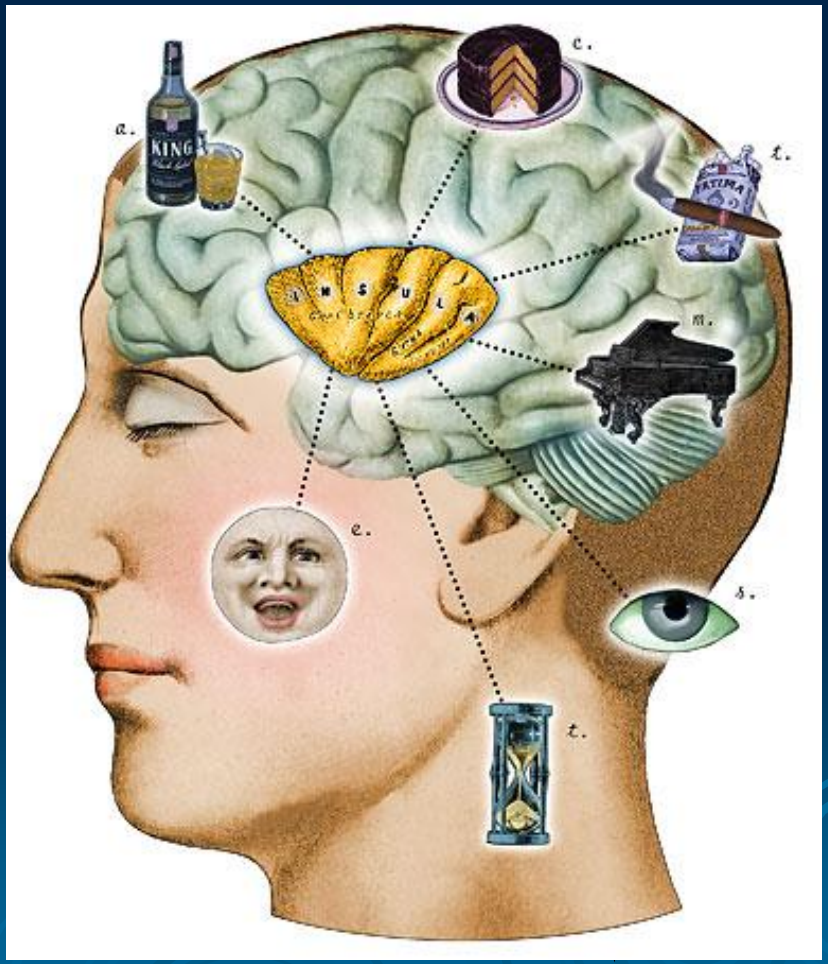
Interim Summary for Cannabinoid system

- CB_1: good target, but the inverse agonist Rimonabant had some side effects
- CB_2: not a good target for nicotine
- Ligands elevating anandamide: potential novel strategy for relapse prevention ?

- Experimental approach #2

INSULAR CORTEX

Another Target: The Insula



The insula as a novel target

Naqvi et al. 2007: Damage to the Insula Disrupts Addiction to Cigarette Smoking.

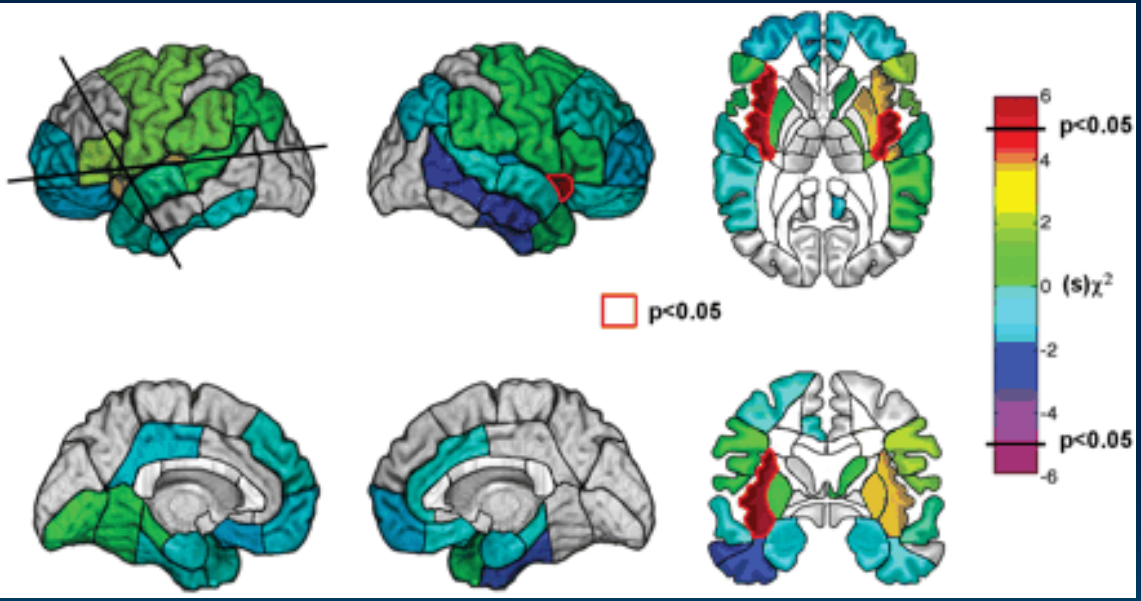
Smokers with brain damage involving the insula were more likely than smokers with brain damage not involving the insula to undergo a disruption of smoking addiction, characterized by the ability to quit smoking easily, immediately, without relapse, and without persistence of the urge to smoke (retrospective self-report).

One patient in their sample quit smoking immediately after he suffered a stroke that damaged his left insula. He stated that he quit because his "body forgot the urge to smoke".

Patients with insular cortex damage reported no decrease in food intake or desire to eat and no less pleasure in eating.

Damage to the Insula Disrupts Addiction to Cigarette Smoking

Nasir H. Naqvi,[1] David Rudrauf,[1,2] Hanna Damasio,[3,4] Antoine Bechara[1,3,4]*

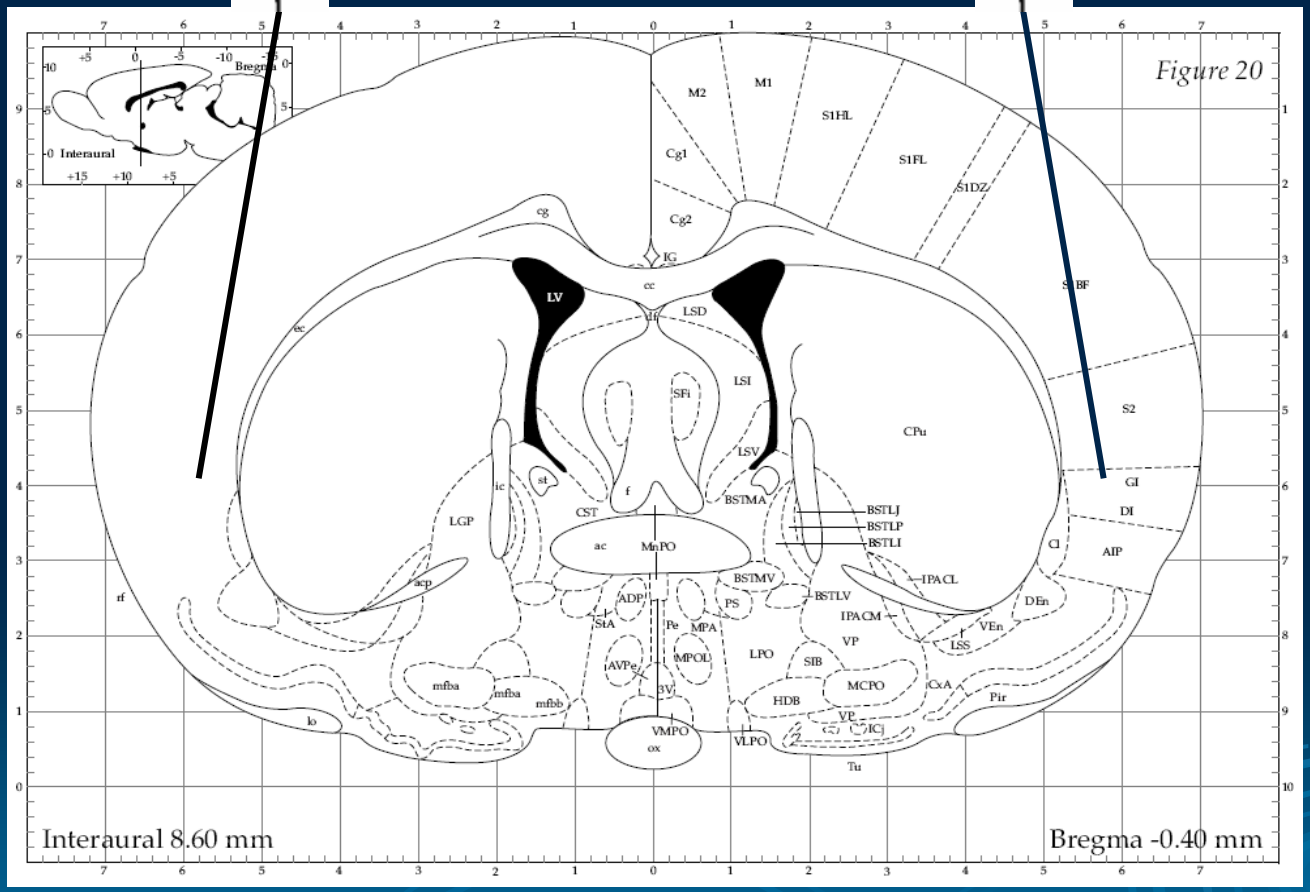


26 JANUARY 2007 VOL 315 SCIENCE www.sciencemag.org

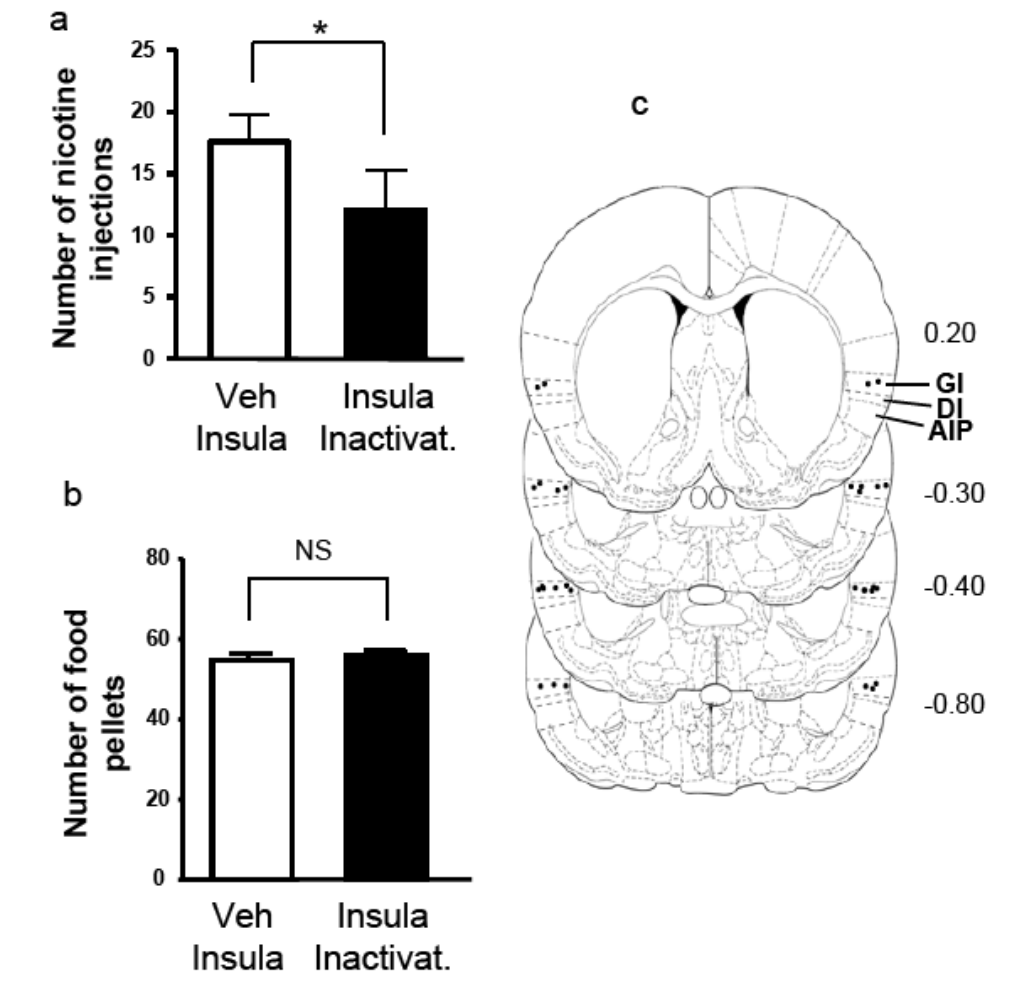
Whole-brain region-by-region logistic regression analysis. Association between a lesion and a disruption of smoking addiction ($P < 0.05$, uncorrected) are highlighted in red. The insula is the only region on either side of the brain where a lesion was significantly associated with a disruption of smoking addiction.

Materials and Methods

Injection of a GABA agonists mix (0.3 nmol Baclofen + 0.03 nmol Muscimol) in 0.5 µl per side

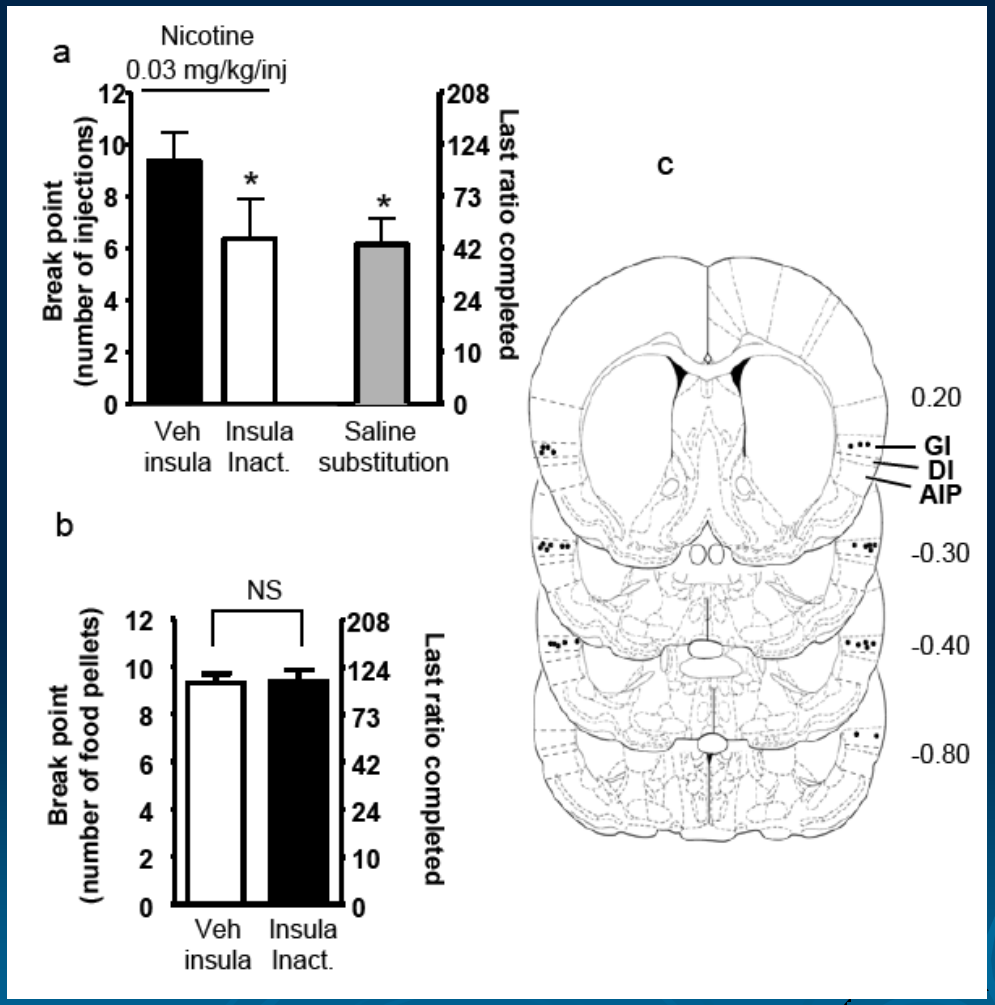


Insula inactivation reduces nicotine-taking, but not food taking under FR5



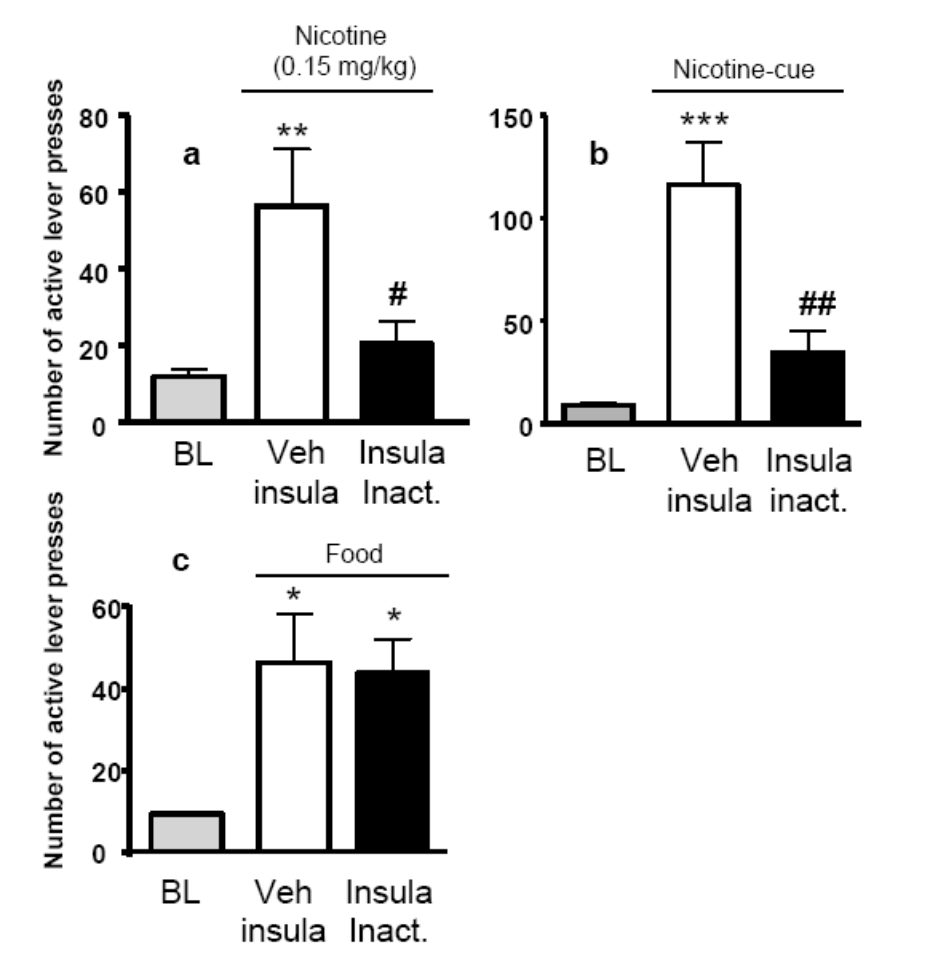
From Forget *et al., 2010*

Insula inactivation reduces motivation for nicotine, but not motivation for food



From Forget *et al., 2010*

Insula inactivation reduces reinstatement for nicotine, but not for food



From Forget *et al., 2010*

Is inactivation a reasonnable goal ? Will it predict effect of DBS/rTMS?

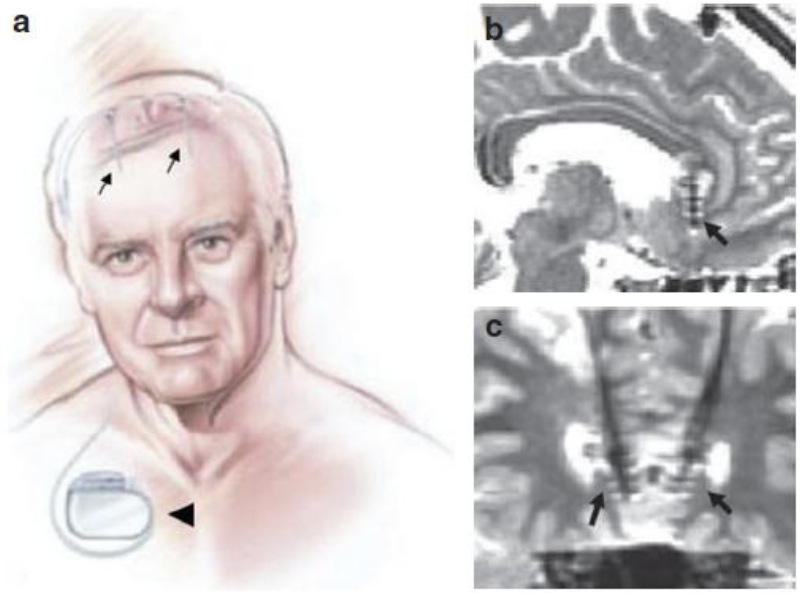
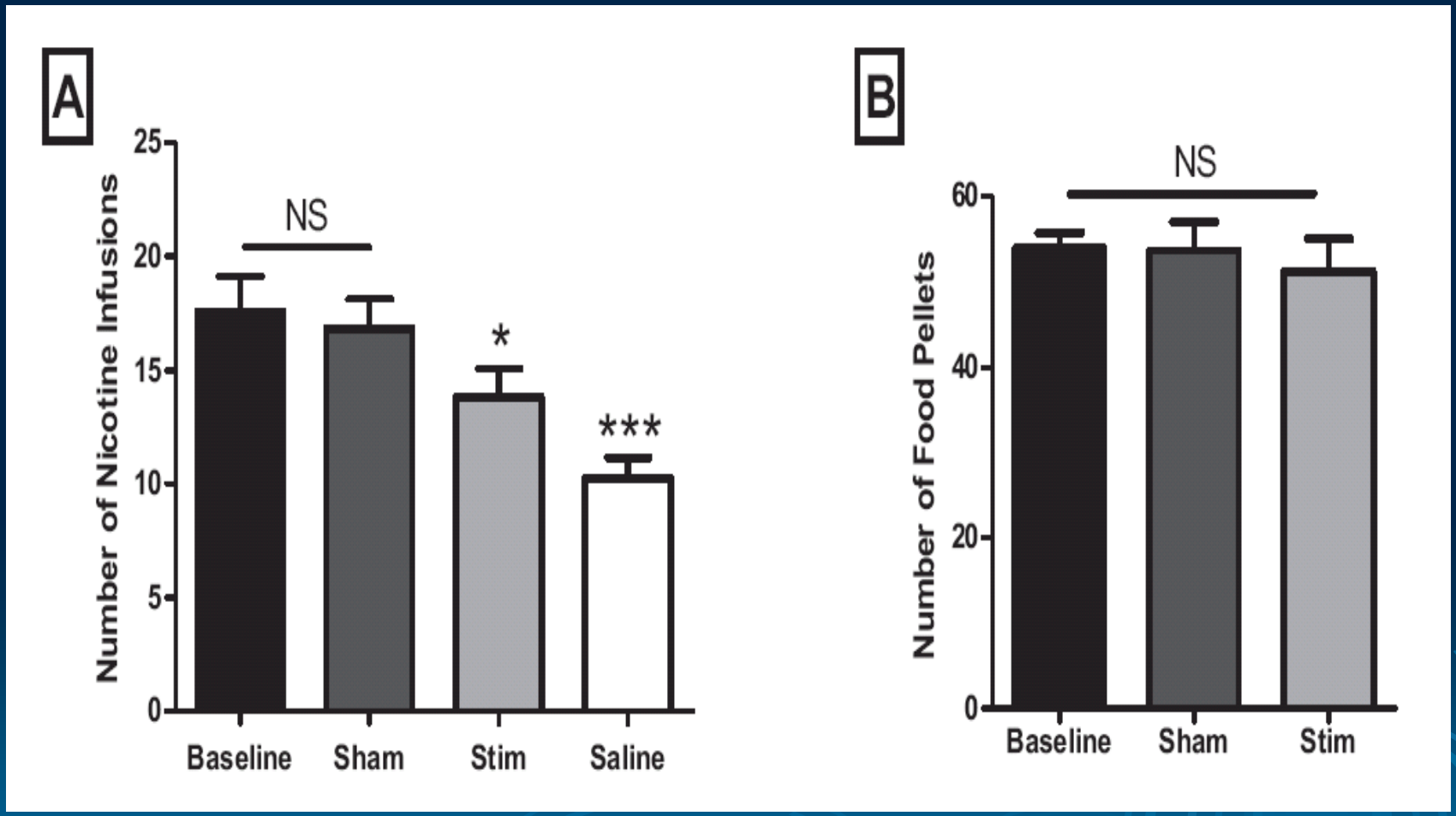


Figure 1 Deep brain stimulation system. (**a**) Schematic representation of a deep brain stimulation system as implanted in a patient. Electrodes (arrows) placed into the brain parenchyma deliver pulses via a pulse generator (arrowhead) (© 2010 Medtronic, Inc.). In **b** and **c**, sagittal and coronal magnetic resonance images of electrodes (arrows) implanted in the subgenual cingulate gyrus in a patient with depression (reprinted from ref. 20 with permission from Elsevier).

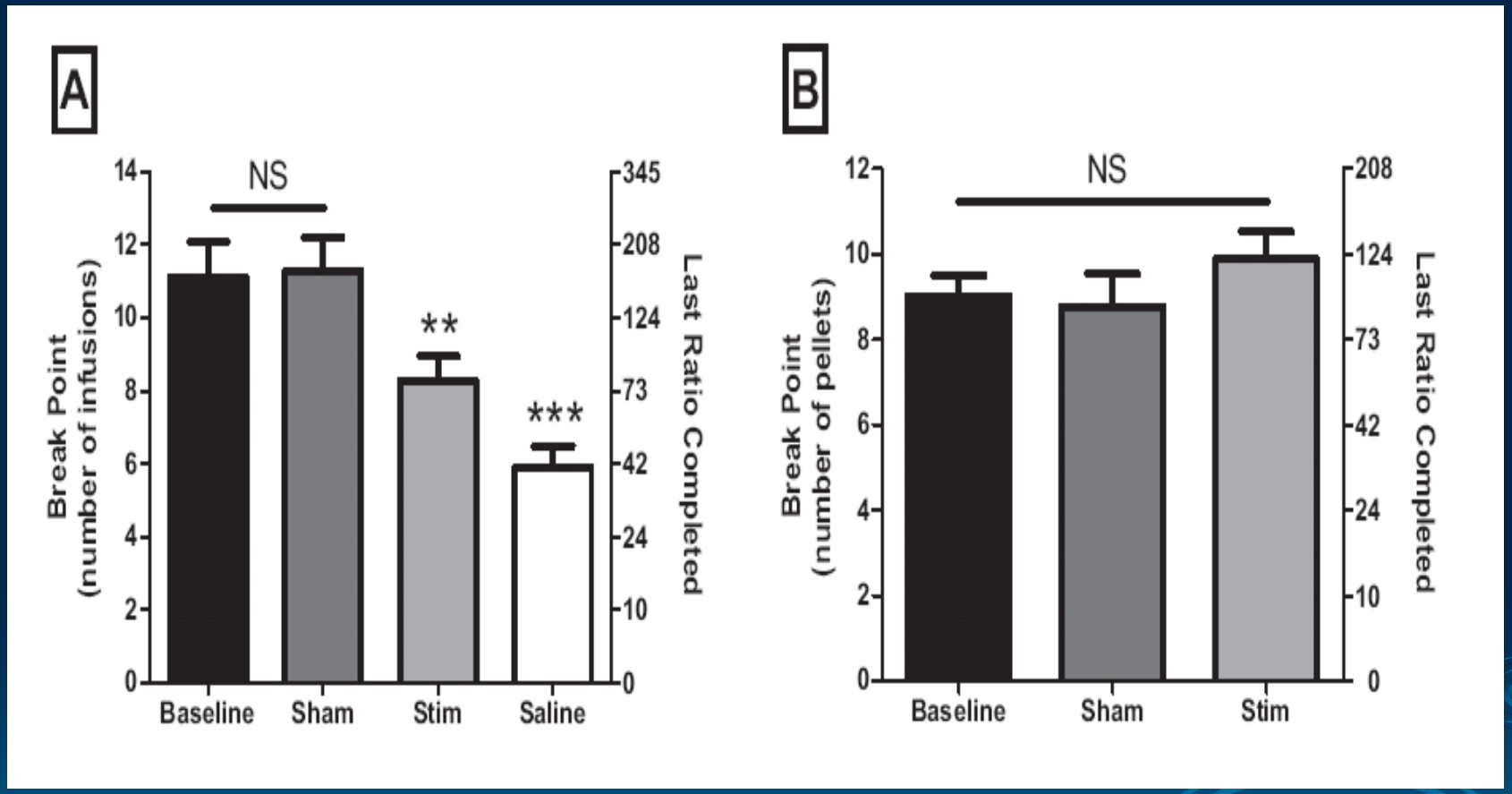
From Hamani *et al., 2010*

Insula DBS reduces nicotine-taking, but not food taking under FR5



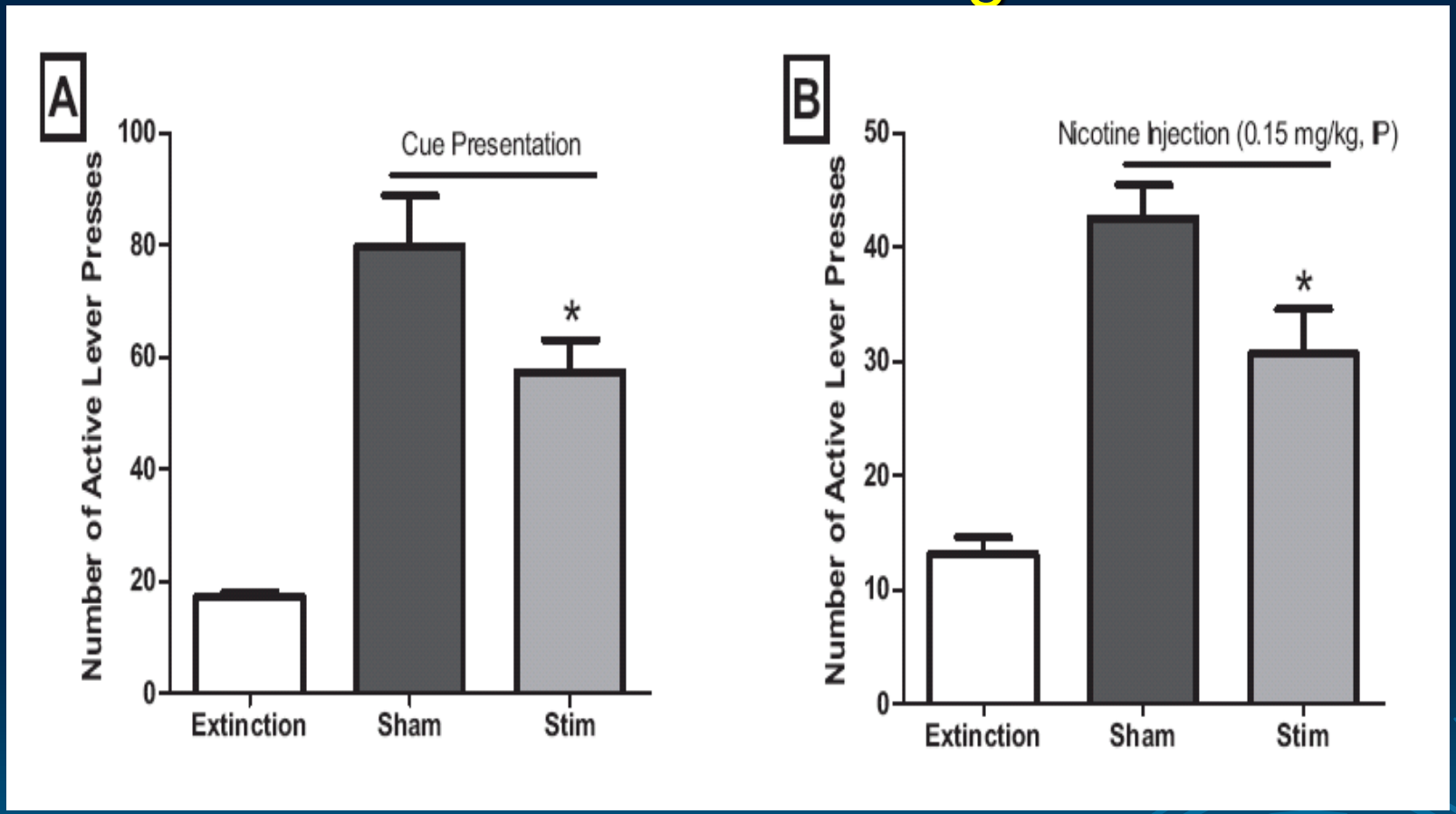
From Pushparaj *et al., 2013*

Insula DBS reduces motivation for nicotine, but not motivation for food



From Pushparaj *et al., 2013*

Insula DBS reduces reinstatement for nicotine-seeking



From Pushparaj *et al., 2013*

Interim conclusion:

inactivation/modulation of insular cortex appears to be promising

DBS appears not practical, but non invasive approaches such as TMS could allow to intervene on this brain structure

Translational Addiction Research

- **Going back and forth between bench and bedside: allow to validate approaches**
- **We have tools allowing us to explore the substrates of drug addiction in animals/humans**
- **Targeting systems that have shown to be involved in humans such as the cannabinoid system and the insula may reduce the risk of failure to translate into effective intervention**

Acknowledgements

Translational Addiction Research Laboratory
Yijin Yan, PhD
Khaled Maram, MD Ms
Yann Le Strat, MD
Saul Lev Ran, MD
Gamaladdin, Islam MD
Pushparaj, Abhiram, Ms
Genane Loheswaran, Ms
Thulasi Thiruchelva, Bs
Greg Staios, Ms
Munmun Chatterjee, PhD
Benoit Forget, PhD

Alcohol Research and Treatment Clinic
Shannon Green, Manager
Kam Balchand, MD
Lisa Lefebvre, MD
Andriy Samokhvalov, MD PhD
Andrew Smith, MD
All staff

Chemist collaborators:
France: Bioprojet, Schwartz Sokoloff
Germany: Holger Stark
Hungary: Gaal and Varga
US NIH: Amy Newman
US: makriyannis

PET Centre
Alan Wilson
Isabelle Boileau
Ariel Graff
Sylvain Houle

Collaborating CAMH Researchers: Daskalakis, George, Selby, Brands, Thomas, Mann, **Hamani**

camh
Centre for Addiction and Mental Health
Centre de toxicomanie et de santé mentale

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

NIDA-IRP: Goldberg Steven,
Justinova Zuzana

INSERM Unit 109: Pierre Sokoloff, Jean-Charles Schwartz, Jorge Diaz

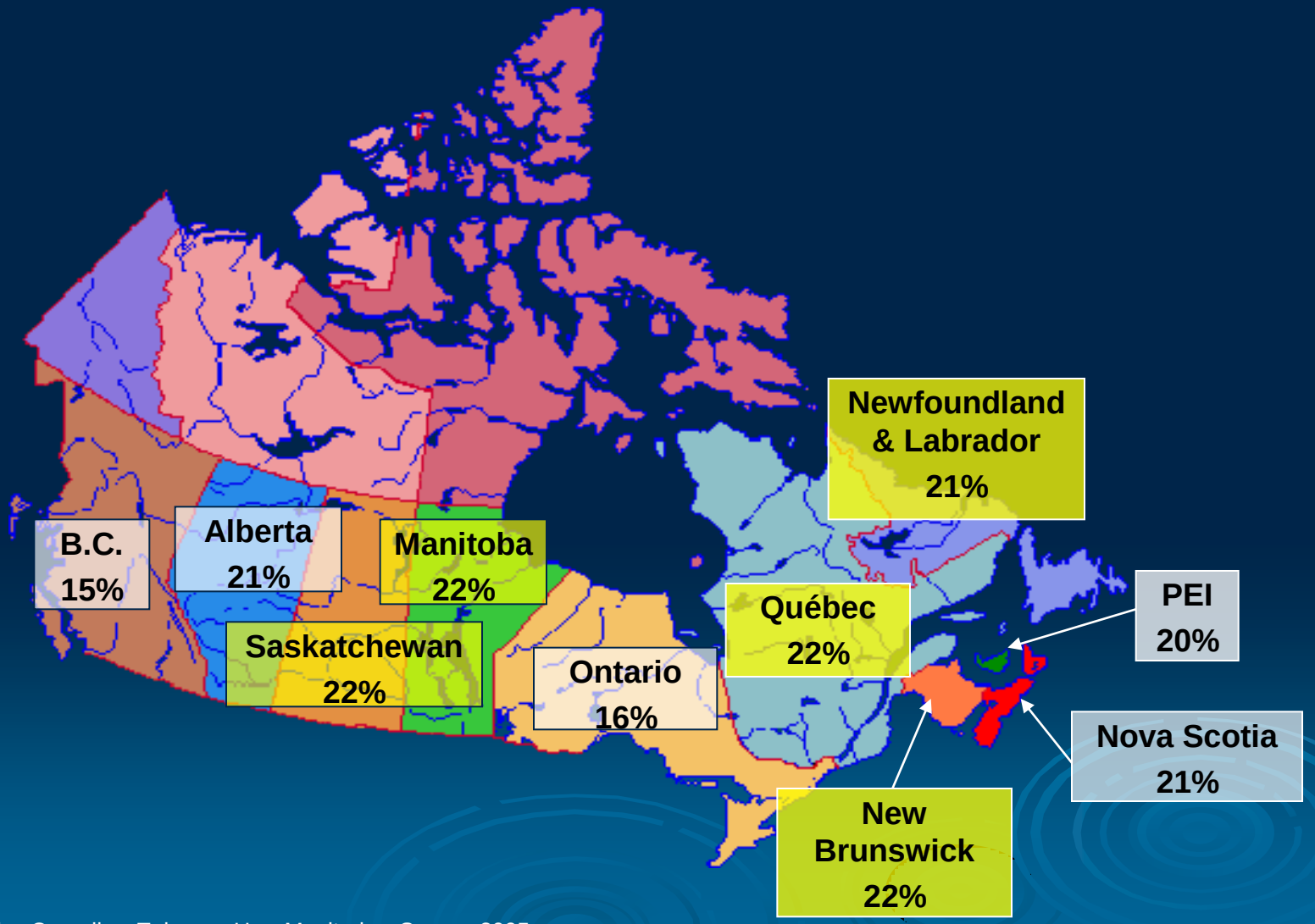
Questions?

Ranking of overall harm based on disability adjusted life years

	Total illicit drugs DALYs		Total alcohol DALYs		Total tobacco DALYs	
	Number (000s)	%	Number (000s)	%	Number (000s)	%
Africa	1131000	0·3	7759000	2·1	1930000	0·5
Americas	3110000	2·2	13102000	9·1	8837000	6·1
Europe	2395000	1·6	17342000	11·4	17725000	11·7
Eastern Mediterranean	2117000	1·5	763000	0·5	2793000	2·0
Southeast Asia	2585000	0·6	12066000	2·7	12764000	2·8
Western Pacific	1886000	0·7	18393000	6·9	12848000	4·8
Global DALYs	13223000	0·9	69424000	4·5	56897000	3·7

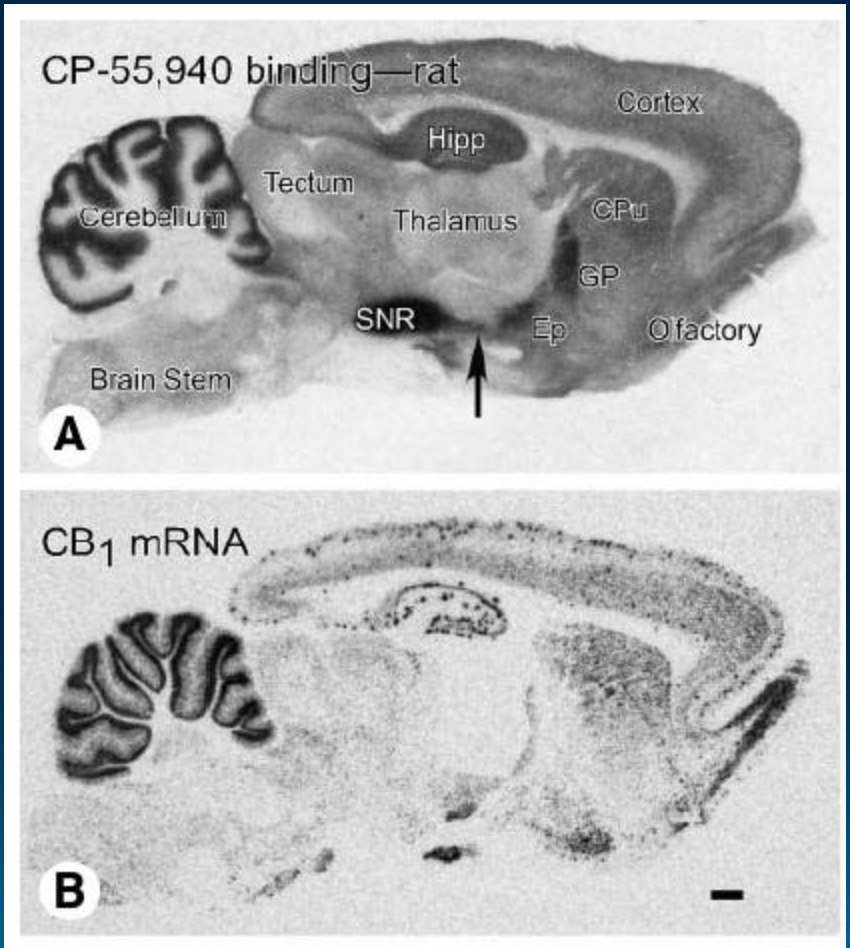
From Degenhard et al, 2012, Lancet

Smoking Prevalence in Canada: 19%
Almost 5 Million Smokers



Health Canada. Canadian Tobacco Use Monitoring Survey 2005, Summary of Annual Results.

CB1 Receptors are widely distributed in the brain

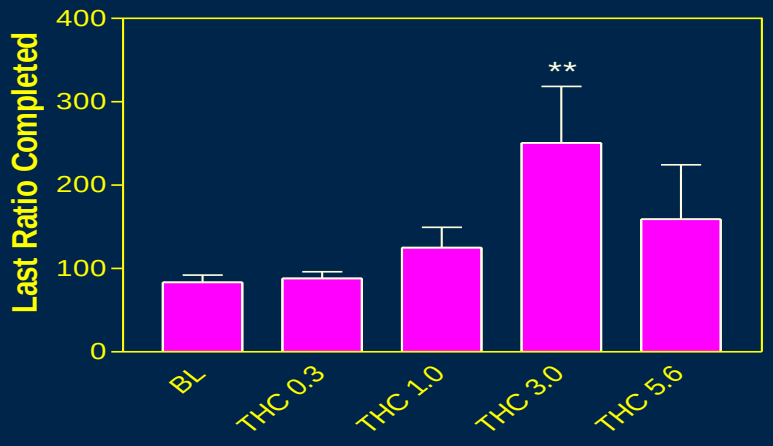


High density in brain areas concerned with memory, cognition, motor coordination and reward

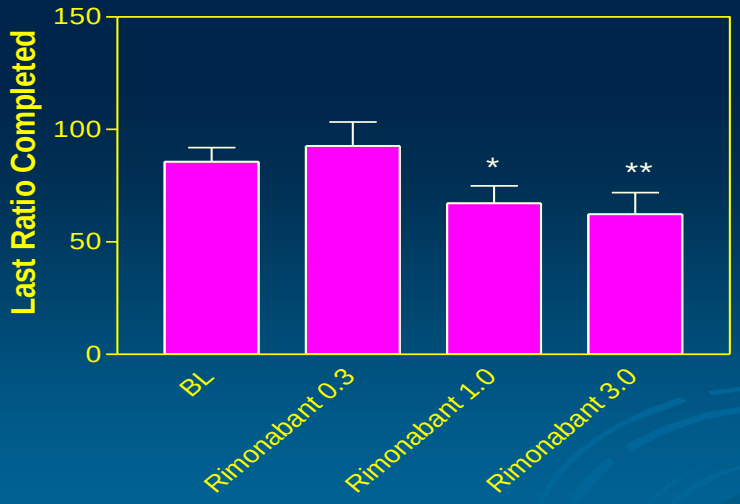
and appetite !!

From Freund et al., 2003

Cannabinoids and the motivation to respond for food in rats



- THC increases the motivation to respond for food



- The CB1 antagonist Rimonabant decreases the motivation to respond for food

Solinas and Goldberg, 2005 *Neuropsychopharmacology*