Optimizing Pharmacotherapy for Smoking Cessation

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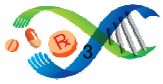
Outline

- What is peculiar about nicotine?
- What criteria may we use to stratify smokers for treatment?
- What are the currently approved smoking cessation products and how do they work?
- What are the unmet needs and how may we meet our challenge?

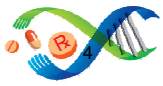
Nicotine Addiction: The Good Signs

- A complex, multifactorial, chronic substance abuse condition prone to relapse
- Synergy of behavioral and pharmacologic interventions beneficial
- Prime candidate for personalized medicine – matching pharmacologic tools with disease profile
- Bupropion SR and varenicline as therapeutic turning point
- Neural imaging to map underlying pathology in order to plan and monitor therapy
- Commitment of public health officials



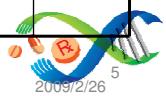
The Challenge

- A complex, multifactorial, chronic substance abuse condition prone to relapse
- Trans-ministry alliance to foster innovations in education and training as well as multidisciplinary research and discovery
- Translation of mechanistic discoveries into pharmacologic innovations to prevent smoking and to sustain abstinence (to interrupt abstinence-relapse cycle)

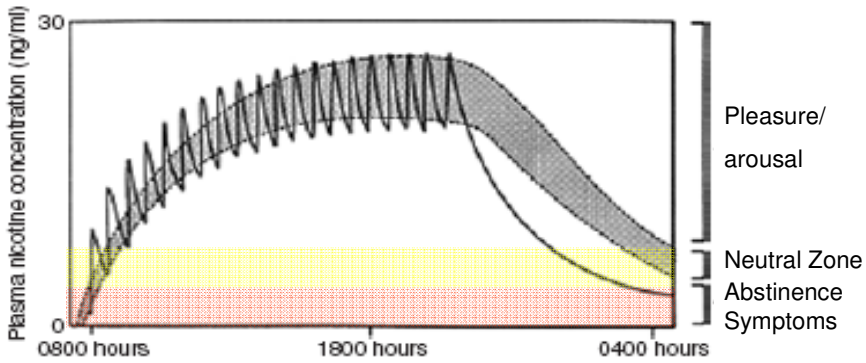


Each Smoker is Unique!

Intake	Chinese-Americans (n=37)	Latinos (n=40)	Whites (n=54)	P
Cigarettes smoked/day	11.2 ± 8.0	12.0 ± 7.8	20.2 ± 12.2	<.001
Daily intake of nicotine, mg	7.7 ± 6.2	12.3 ± 10.4	20.5 ± 14.8	.011
Nicotine intake/ cigarette, mg	0.73 ± 0.55	1.05 ± 0.63	1.10 ± 0.72	.039

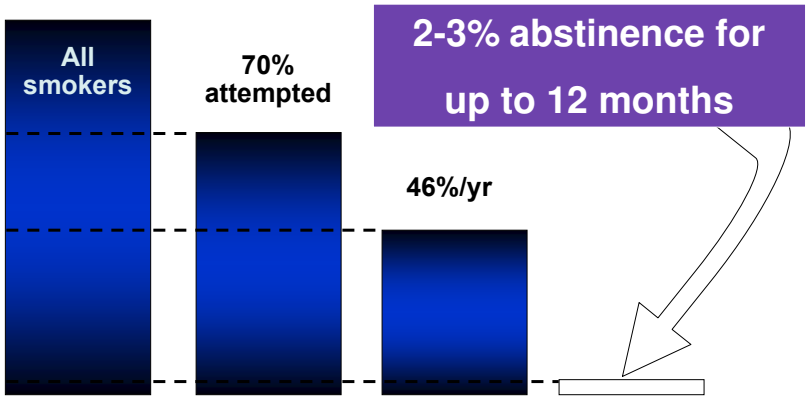


Model for the nicotine addiction cycle during daily cigarette smoking

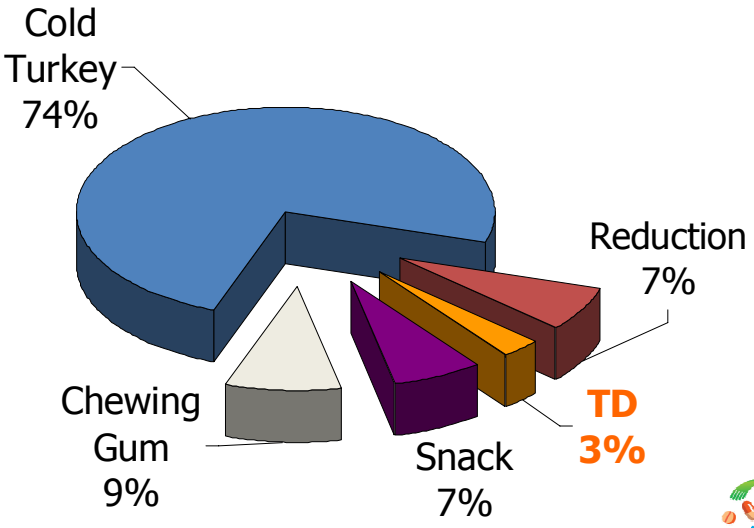


The Curse of Addiction

(6-9 Attempts)



Centers for Disease Control ad Prevention. Cigarette smoking among adults – US, 1993. MMWR 1994;43:925-9.
Fiore M, et al. Clinical Practice Guidelines: Treating Tobacco Use and Dependence US Dept Health and Human Services, PHS 2000.
Centers for Disease Control ad Prevention. Smoking cessation during previous year among adults – US, 1990 and 1991. MMWR 1993; 42:504-7.



Mean plasma nicotine concentrations when smoking cigarettes of differing nicotine content and usual brand (UB) (n=12)

Onset 10 sec

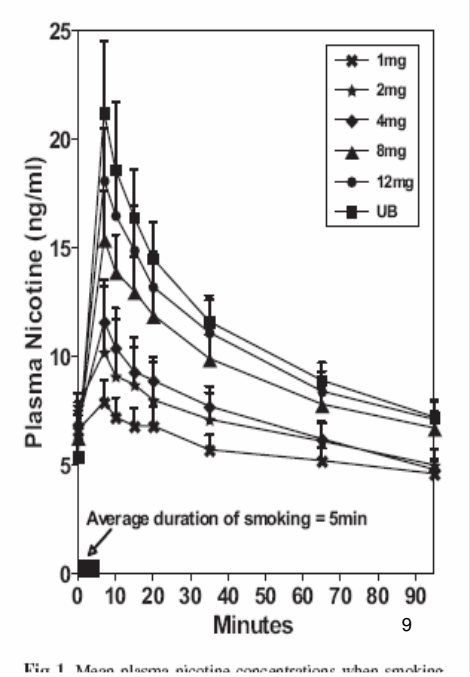
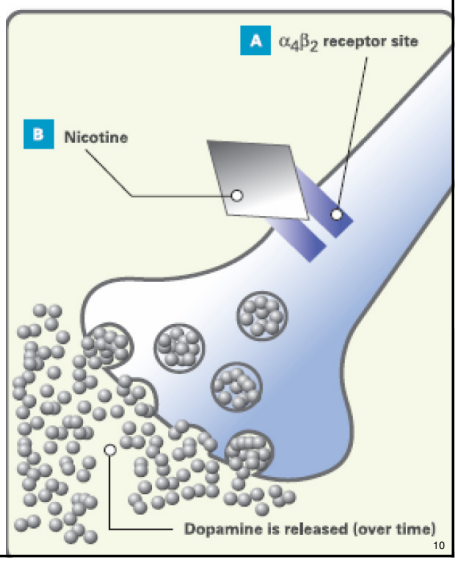
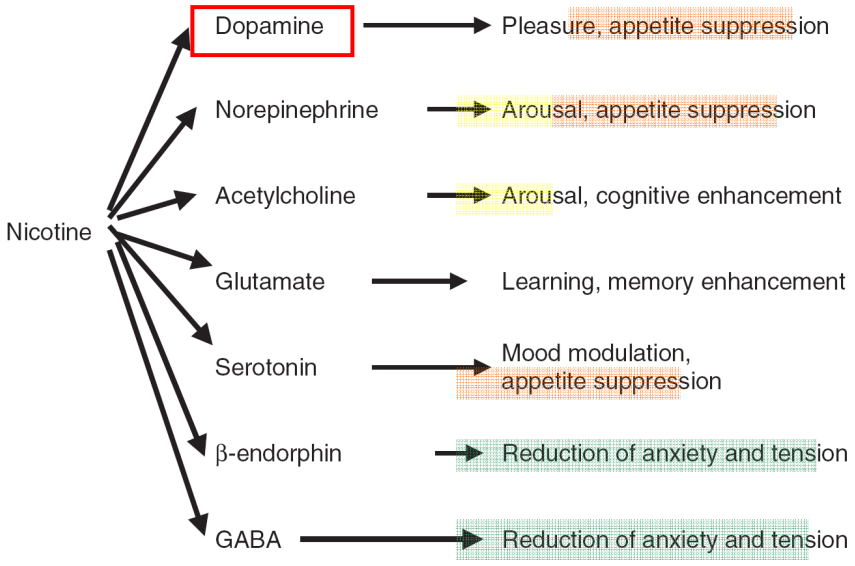


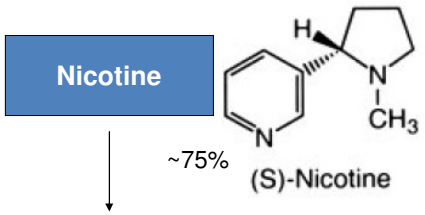
Fig 1. Mean plasma nicotine concentrations when smoking

Nicotine Action at the Receptor

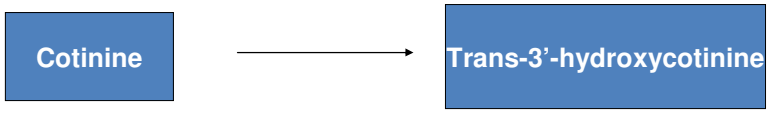


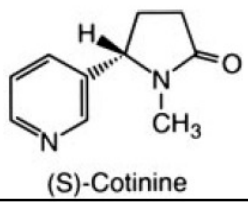


Nicotine Metabolism: >95% Total Body Clearance

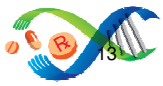


Half-life ~ 120 mins.
CYP2A6



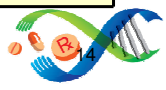


Addiction	Nicotine Metabolism	Dopamine Levels
Low	Reduced	Increased
High	Increased	Reduced



FDA Approved Smoking Cessation Medications

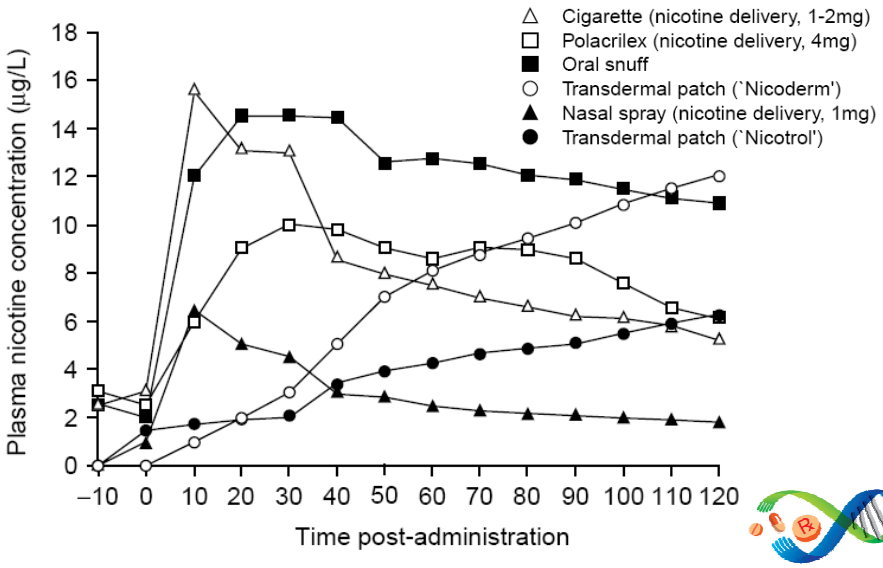
Nicotine Replacement Therapy		Other Approaches
	Nasal Spray	
Inhaler		
Gum		
Lozenge		Bupropion SR
	Patch	Varenicline



Biopharmaceutics of Administration Routes

Mucosa	Release	Permeability	Surface Area	Flux
Lung	++++	++	++++	1
Nose	+++	++++	+	2
Oral cavity	++	++	++	3
Skin	+	+	++	4

Nicotine Replacement Therapy (NRT): Nicotine Delivery by Cigarettes and NRT Products



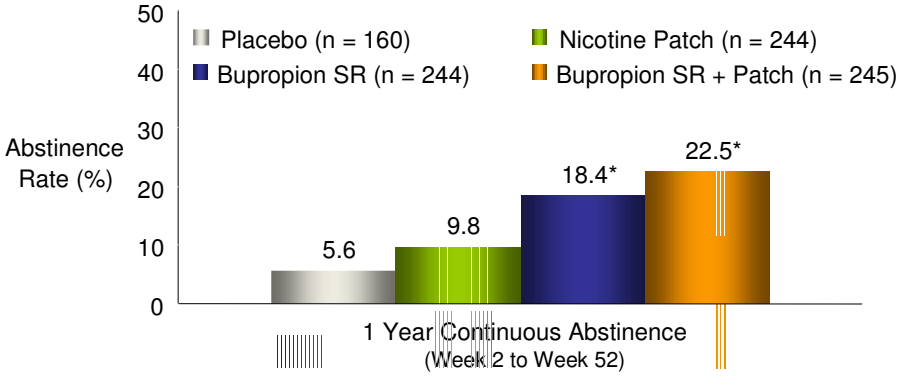
Sweeney CT, et al. *CNS Drugs*. 2001;15:453-467.

Efficacy of Nicotine Replacement Therapy (NRT)

Comparison	N Trials	N Participants	Pooled OR (95% CI)
Gum	52	17,783	1.66 (1.52–1.81)
Patch	37	16,691	1.81 (1.63–2.02)
Nasal spray	4	887	2.35 (1.63–3.38)
Inhaler	4	976	2.14 (1.44–3.18)
Tablets/lozenges	4	2739	2.05 (1.62–2.59)
Combination vs single type	7	3202	1.42 (1.14–1.76)
Any NRT vs control	103	39,503	1.77 (1.66–1.88)

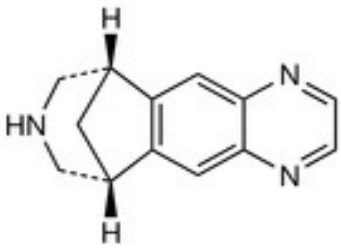
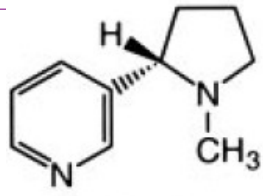
1. Silagy C et al. *Cochrane Database Syst Rev.* 2004;(3):CD000146. 2. Stead L, Lancaster T. *Int J Epidemiol.* 2005;34:1001–1003.

Comparison of Nicotine Replacement Therapy (NRT) and Bupropion SR Therapy for Quitting Smoking[1]



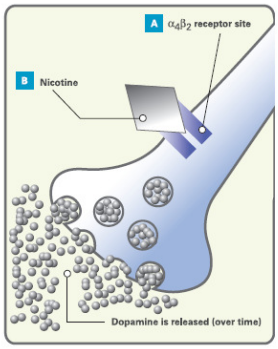
*$P \leq 0.001$ vs placebo and patch alone.

1. Jorenby DE, et al. *N Engl J Med.* 1999;340:685–691. 2. Talwar A et al. *Med Clin North Am.* 2004;88:1517–1534.

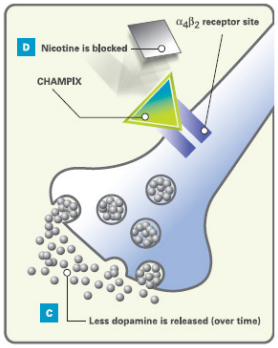
		
	Varenicline	(S)-Nicotine
MW	211.2	162
$T_{1/2}$ (hrs)	24	2

Mechanism of Action

Nicotine action at the receptor



CHAMPIX is a partial agonist



Based on animal models and in vitro studies. For illustrative purposes only.

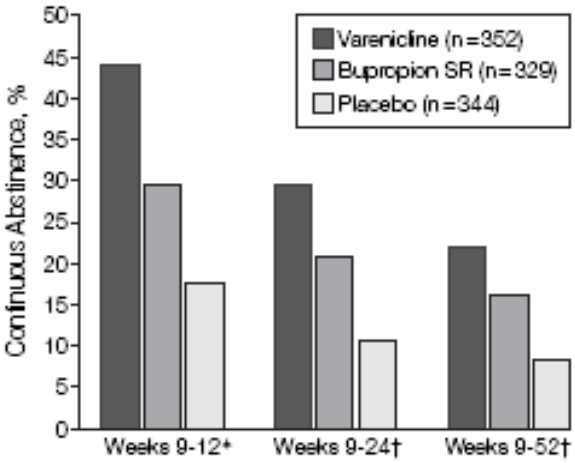
A $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChRs) in the brain mediate reinforcement- and dependence-producing effects of nicotine.[10,11]

B Nicotine binds to the receptor, stimulating the release of dopamine, for a full agonist effect.[12]

C CHAMPIX binds to, and partially stimulates, the receptor without creating a full nicotine effect on the release of dopamine **(agonist effect)**.

D When CHAMPIX binds to $\alpha_4\beta_2$ nAChRs, it blocks the ability of nicotine to stimulate the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking **(antagonist effect)**.

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 (bupro-

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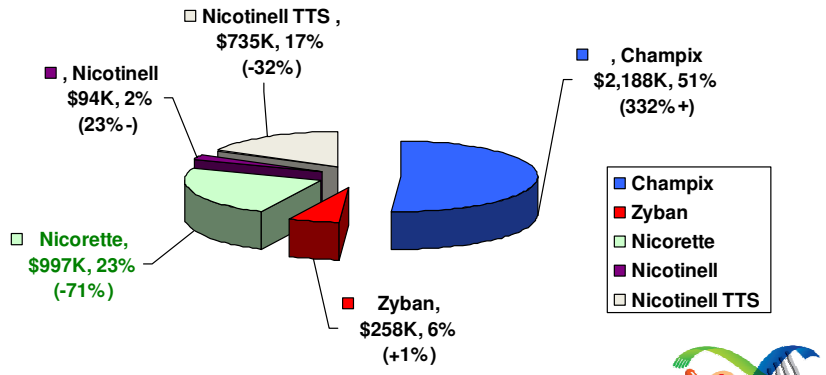
Market Share in N7B Market (HKIMS 2008 Jan–Sept Data)

Total Market in 2008 Jan to Sept

= HK$4,272K (21% ↓)



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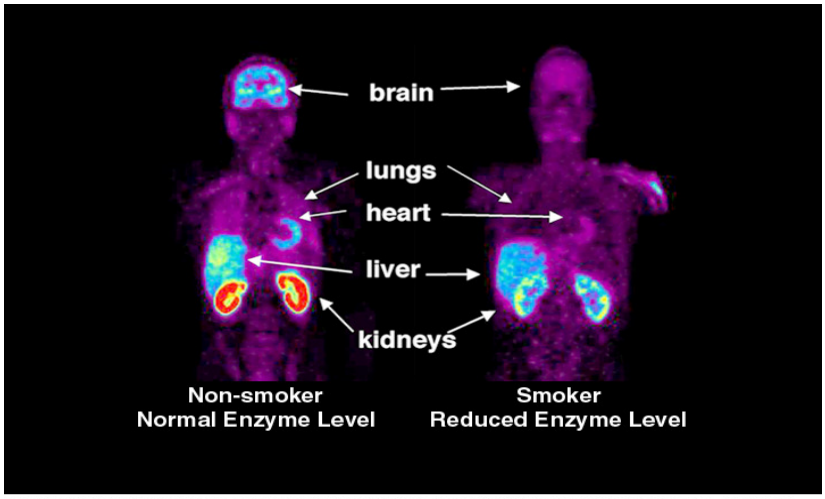
Functional Brain Imaging

- To determine the relationships between brain function and effects of acute and chronic and cigarette smoking and of smoking-related behaviors

Functional Brain Imaging

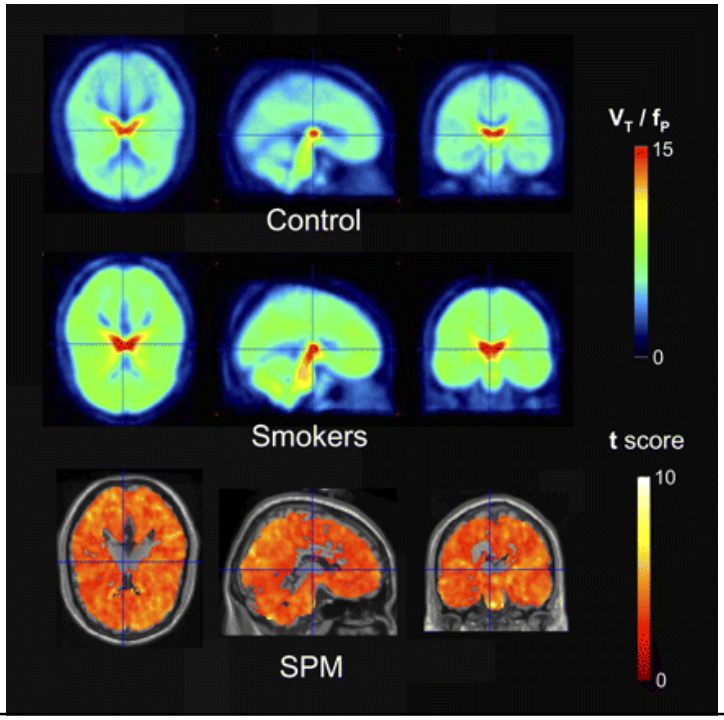
- Functional magnetic resonance imaging (fMRI)
- Positron emission tomography (PET)
- Single photon emission computed tomography (SPEC)
- Autoradiography

Imaging

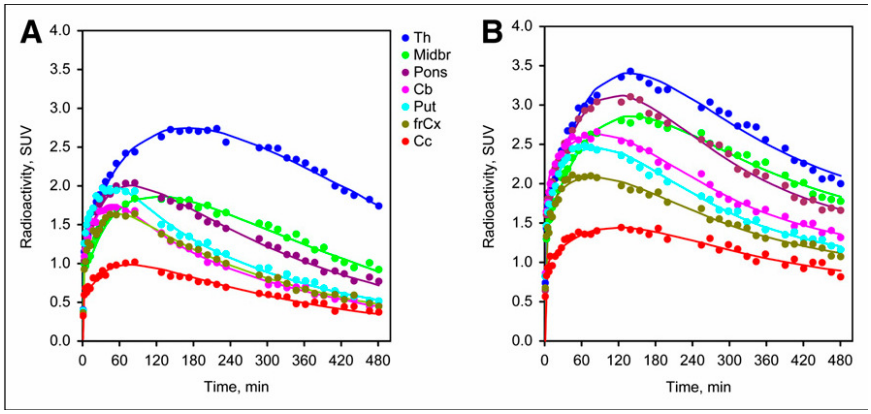


The illustration shows the concentration of radioactive tracer bound to monoamine oxidase B (MAO B). Red shows the highest concentration. Clearly, lower concentrations are seen in the smoker. In certain areas, such as the lungs and brain, concentrations are so low as to be virtually absent. This demonstrates decreased amounts of MAO B in the peripheral organs of smokers compared with nonsmokers.

Proceedings of the National Academy of Sciences, September 8, 2003, "Low Monoamine Oxidase B in Peripheral Organs in Smokers."



Representative Time-activity Curves for Several Brain Regions in (A) Nonsmokers (B) Smokers



- Smokers who carry genetic polymorphisms associated with reduced nicotinic receptor (and possibly also dopaminergic) activity may experience greater benefit from the greater rewarding effects of nicotine spray (NS).
- Smokers with increased activity variants in the -opioid receptor (MOR) may have better success with the higher levels of nicotine delivered by transdermal nicotine patches (TN).

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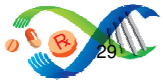
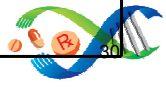
Hurdles to New Drug Development

Market-size perceptions	
Problems	**Potential Solutions**
▸ Variable drug response in subpopulations may limit the probability of one-size-fits-all approaches ▸Medications may not be covered by health plans ▸Existing medications priced disproportionately high compared with cigarettes	▸Combinations of medications may have better efficacy in particular groups ▸Pharmacogenetic research that identifies subpopulations with variable response may reduce the market share but targeted therapy will improve effectiveness rates ▸Health economic research to document costs of medication relative to tobacco use.

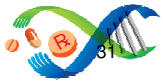


Mechanism of Action	
Problems	**Potential Solutions**
▸ Our understanding of the pathophysiology of nicotine dependence is rather rudimentary. ▸Genetics of dependence and response to therapeutic intervention	▸Funding agencies could explicitly encourage broader efforts to elucidate other CNS circuits and other behavioral mechanisms (**funding from TAX increase**) ▸Broaden approach to focus on reduction of subjective negative effects of abstinence ▸Go beyond single gene



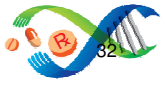
Testing Tools

Problems	Potential Solutions
▸ Lack of tools at all levels of analysis: from non-human preclinical to human experimental and early Phase I.	NIH Roadmap for Medical Research initiatives in libraries including assays for screening
▸Limited library of compounds to provide positive predictive validity for new assays	▸Investing more resources in the development and validation of better models for evaluating potential medications for nicotine



The Time to Act is Now

- The number of smokers is expected to rise to 1.4-1.5 billion by 2010 and 1.6-1.9 billion in 2025.
- To better understand how the social, physical, and cultural environments and genes interact to determine a person's use of and, possibly, eventual addiction to tobacco
- Transdisciplinary effort



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