
NICOTINE AND DRUG INTERACTIONS

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ABRUPT SMOKING CESSATION CAN AFFECT THE METABOLISM OF DRUGS.

- ✗ When patients enter hospital they may have to stop smoking abruptly if the hospital has a 'no smoking' policy.
- ✗ Cigarette smoking induces the activity of human cytochromes P450 (CYP) 1A2 and 2B6.
- ✗ Decreased CYP1A2 activity after smoking cessation increases the risk of adverse drug reactions, with reports of increased toxicity from clozapine and olanzapine.
- ✗ Predicting the required dose reduction of drugs metabolised by CYP1A2 after smoking cessation is challenging. Therapeutic drug monitoring should be used when possible
- ✗ Nicotine replacement therapy does not influence CYP1A2 activity

NICOTINE EFFECTS:

- ✗ Nicotine increases blood pressure and heart rate.^[1]
- ✗ Nicotine can also induce potentially atherogenic genes in human coronary artery endothelial cells.^[2]
- ✗ Microvascular injury can result through its action on nicotinic acetylcholine receptors (nAChRs).^[3]
- ✗ Nicotine elevates serum cholesterol levels, supports clot formation, and aids in plaque formation by enhancing vascular smooth muscle.^[4]

1. Sabha M, Tanus-Santos JE, Toledo JC, Cittadino M, Rocha JC, Moreno H (August 2000). "Transdermal nicotine mimics the smoking-induced endothelial dysfunction". *Clinical Pharmacology and Therapeutics* **68** (2): 167–74.
2. Zhang S, Day I, Ye S (February 2001). "Nicotine induced changes in gene expression by human coronary artery endothelial cells". *Atherosclerosis* **154** (2): 277–83.
3. Hawkins BT, Brown RC, Davis TP (February 2002). "Smoking and ischemic stroke: a role for nicotine?". *Trends in Pharmacological Sciences* **23** (2): 78–82.
4. Jerry JM, Collins GB, Strem D (2015). "E-cigarettes: Safe to recommend to patients?". *Cleve Clin J Med* **82** (8): 521–6.

THE CHEMICALS IN SMOKE MAY INTERACT

- × via pharmacokinetic and pharmacodynamic (often nicotine-mediated) mechanisms with:
 - + antipsychotics,
 - + antidepressants,
 - + benzodiazepines,
 - + oral contraceptives,
 - + inhaled corticosteroids
 - + beta blockers

[Kroon LA. Drug interactions with smoking. Am J Health Syst Pharm 2007;64:1917-21](#)

CYTOCHROMES

- ✗ Cytochrome P450 enzymes function to metabolize potentially toxic compounds, including [drugs](#) and products of endogenous metabolism
- ✗ CYPs are the major enzymes involved in [drug metabolism](#), accounting for about 75% of the total metabolism.^[1] Most drugs undergo deactivation by CYPs, either directly or by facilitated [excretion](#) from the body. Also, many substances are [bioactivated](#) by CYPs to form their active compounds.
- ✗ Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme ([enzyme induction](#)) or by directly inhibiting the activity of the CYP ([enzyme inhibition](#)). This is a major source of adverse [drug interactions](#), since changes in CYP enzyme activity may affect the [metabolism](#) and [clearance](#) of various drugs.

ENZYMES INDUCED BY TOBACCO SMOKING

- ✗ cytochrome P450 (CYP) 1A1, CYP1A2 and possibly CYP2E1:
- ✗ CYP1A1 is primarily an extrahepatic enzyme found in lung and placenta
 - + CYP1A1 high inducibility is more common in patients with lung cancer
- ✗ CYP1A2 is a hepatic enzyme responsible for the metabolism of a number of drugs and activation of some procarcinogens
 - + Caffeine demethylation
- ✗ significantly enhances CYP2E1 activity - this enzyme metabolises a number of drugs as well as activating some carcinogens
 - + as measured by the clearance of chlorzoxazone.

CIGARETTE SMOKING...

- ✗ induces metabolism of several drugs:
 - + theophylline,
 - + caffeine,
 - + tacrine,
 - + imipramine,
 - + haloperidol,
 - + pentazocine,
 - + propranolol,
 - + flecainide and
 - + estradiol.
- ✗ results in faster clearance of heparin, (activates thrombosis with enhanced heparin binding to antithrombin III)
- ✗ Slows the rate of insulin absorption (via cutaneous vasoconstriction by nicotine)

CIGARETTE SMOKING ...

- ✗ Due to pharmacodynamic interactions, most likely reflecting the effects of the stimulant actions of nicotine:
- ✗ cigarette smoking is associated with:
 - + a lesser magnitude of blood pressure and heart rate lowering during treatment with beta-blockers,
 - + less sedation from benzodiazepines and
 - + less analgesia from some opioids.

CIGARETTE SMOKING CAN AFFECT THE PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES OF MANY PSYCHOTROPIC DRUGS

- ✗ increase the metabolism and decrease the plasma concentrations of imipramine, clomipramine, fluvoxamine and trazodone.
- ✗ The effect on the plasma concentrations of amitriptyline and nortriptyline is variable.
- ✗ Amfebutamone (bupropion) does not appear to be affected by smoking.
- ✗ increased clearance of tiotixene, fluphenazine, haloperidol and olanzapine.
- ✗ Plasma concentrations of chlorpromazine and clozapine are reduced
- ✗ Clinically, reduced drowsiness in smokers receiving chlorpromazine, and benzodiazepines, compared with nonsmokers has been reported.
- ✗ Increased clearance of the benzodiazepines alprazolam, lorazepam, oxazepam, diazepam and demethyl-diazepam is found in cigarette smokers,
- ✗ chlordiazepoxide does not appear to be affected by smoking.
- ✗ Carbamazepine appears to be minimally affected by cigarette smoke.

BENZODIAZEPINES

- ✖ Nicotine activates the central nervous system and this may explain the attenuated sedation observed in smokers compared to non-smokers taking benzodiazepines.
- ✖ Prescribers should be aware that when patients taking benzodiazepines stop smoking, there is a risk of central nervous system depression.

METHADONE

- ✖ attenuates nicotine withdrawal. Reducing methadone doses when the patient is trying to stop smoking could be detrimental.

WARFARIN (“MAREVAN”)

- ✗ Smoking may increase warfarin’s clearance and reduce its effect.
- ✗ smoking appeared to increase the warfarin dose requirement by 12%, resulting in an extra 2.26 mg per week compared with nonsmoking.
- ✗ Consequently, INR should be closely monitored when there is a change in patients' smoking status.

CAFFEINE

- ✗ is highly dependent on CYP1A2 for its metabolism.
- ✗ Smokers require up to four times as much caffeine as non-smokers to achieve the same plasma caffeine concentration.
- ✗ Caffeine can increase the concentration of clozapine and olanzapine.

COMBINED ORAL CONTRACEPTIVES

- × Smoking increases the adverse effects:
 - + thromboembolism,
 - + ischaemic stroke and myocardial infarction).
- × The combined oral contraceptive pill:
 - + is contraindicated in women aged 35 years or older who smoke 15 or more cigarettes a day.
 - + For smokers who use combined low-dose oral contraceptives, the attributable risk of death from cardiovascular disease is:
 - × 19.4 per 100 000 women aged 35–44 years
 - × (vs 3.03 per 100 000 for non-smoking women of the same age). This risk is also presumed to be associated with other contraceptives containing oestrogen.
- × Limited data suggest no convincing association between cardiovascular disease and progestogen-only pill use. If smoking cessation is unsuccessful, non-hormonal or progestogen-only contraceptives are preferred from a cardiovascular perspective.

[Kroon LA. Drug interactions with smoking. Am J Health Syst Pharm 2007;64:1917-21.](#)

Schwinger PJ, Ory HW, Visness CM. Estimates of the risk of cardiovascular death attributable to low-dose oral contraceptives in the United States. Am J Obstet Gynecol 1999;180:241-9.

INHALED CORTICOSTEROIDS

- ✖ The efficacy of inhaled corticosteroids may be reduced in asthmatic patients who smoke, so these patients might require higher doses of inhaled corticosteroids to attain asthma control.
- ✖ Proposed mechanisms of corticosteroid insensitivity include suppression of histone deacetylase expression and activity by cigarette smoking, causing inflammatory gene expression and a reduction in glucocorticoid function.
- ✖ Clearance of corticosteroids from the lungs may be altered by increased mucus secretion or airway permeability.

Lazarus S, Chinchilli V, Rollings N, Boushey H, Cherniack R, Craig T, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. Am J Respir Crit Care Med 2007;175:783-90

Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax 2002;57:226-30

BETA BLOCKERS

- ✖ Smokers may require higher doses of beta blockers. Although propranolol is a CYP1A2 substrate ([Box](#)), nicotine-mediated central nervous system activation may diminish the effect of beta blockers on blood pressure and heart rate.

INSULIN

- ✖ Sub/cutaneous: Any factors that alter the rate of blood flow through the skin and fat will change insulin absorption. Smoking decreases blood flow.
- ✖ Inhaled insulin (in clinical trials): The amount of insulin absorbed during the first 6 h after dosing was significantly greater in smokers; peak concentration was both higher and earlier in the smokers (time to maximal serum concentration of insulin [t(max)] 31.5 vs. 53.9 min, $P = 0.0003$).

TB TREATMENT

- ✕ the risk of a poor tuberculosis treatment outcome was 70% greater in current smokers compared to never smokers. Patients being treated for MDR tuberculosis had a 3-fold greater risk of a poor outcome compared to patients being treated for other forms of tuberculosis. We also found that patients who had recently stopped smoking had a lower risk of a poor tuberculosis outcome than current smokers.

-
- × Imipramine (Tofranil)
 - × Oxazepam (Serax)
 - × Propranolol (Inderal)
 - × Labetalol (Normodyne, Trandate)
 - × Prazosin (Minipress)
 - × Theophylline (Theo-Dur, Theochron, Theolair)
 - × Pentazocine (Talwin)
 - × Insulin

SUITSETAMISE LÕPETAMINE VÕIB PÕHJUSTADA

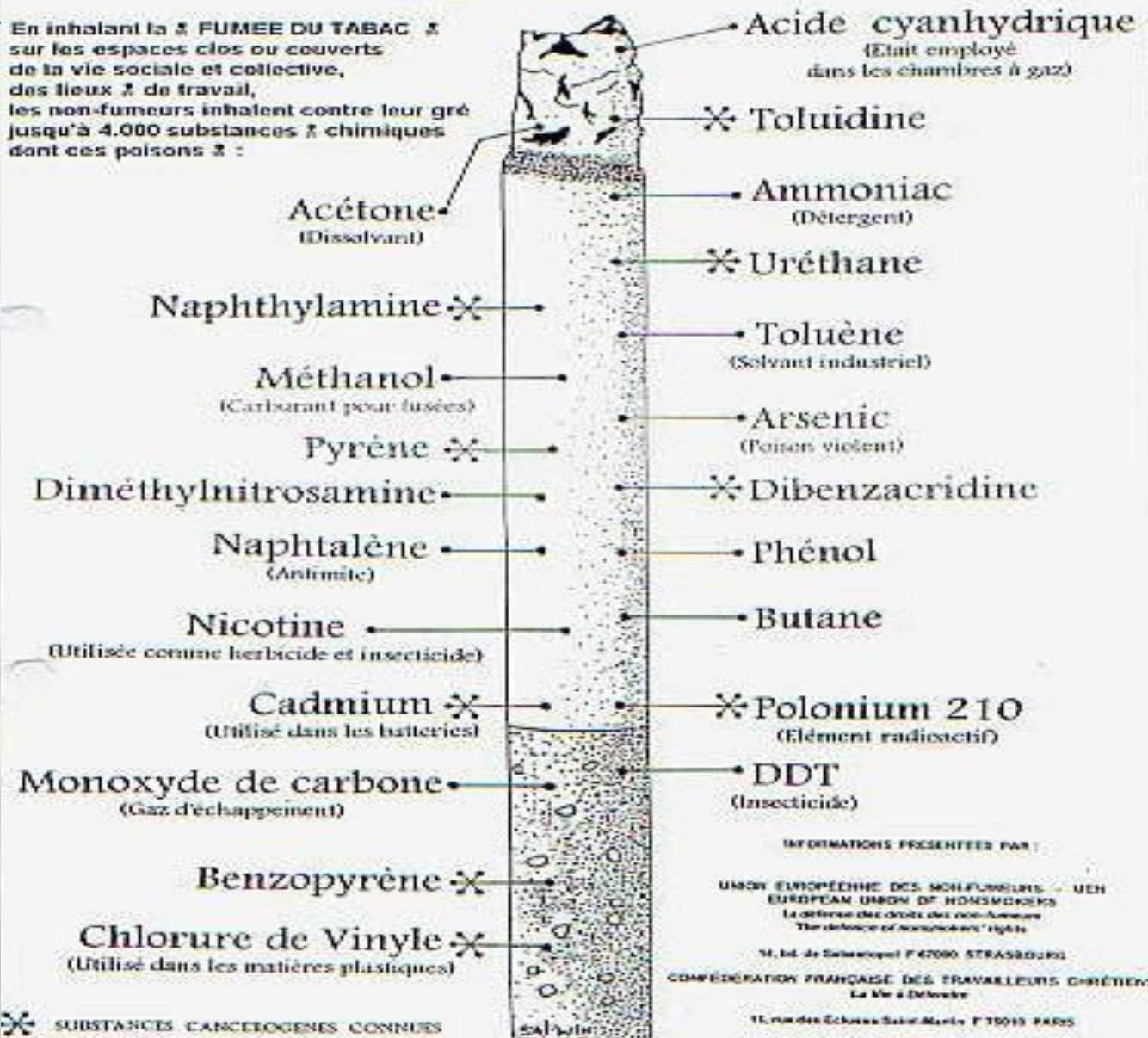
- ✘ metabolismi aeglustumist, mille tulemusena võib vajalikuks osutuda samaaegselt kasutatavate ravimite annuse korrigeerimine. Seda peab silmas pidama ravimite juures, mida katalüüsib CYP1A2 (võimalik, et ka CYP1A1). Nendeks ravimiteks on näiteks kofeiin, teofülliin, flekainiid, takriin, klosapiin ja ropinool. Osaliselt CYP1A2 kaudu metaboliseeruvad ravimid on näiteks imipramiin, olansapiin, klomipramiin ja fluvoksamiin.
- ✘ Piiratud andmed on olemas selle kohta, et flekainiidi ja pentasosiini ainevahetus võib samuti olla indutseeritud suitsetamisest.
- ✘ Kliiniliselt olulisi koostoimeid nikotiini ja teiste ravimite vahel ei ole täheldatud, kuid nikotiin võib tugevdada adenosiini toimet hemodünaamikale



DANGER DE MORT



En inhalant la **FUMÉE DU TABAC** sur les espaces clos ou couverts de la vie sociale et collective, des lieux de travail, les non-fumeurs inhalent contre leur gré jusqu'à 4.000 substances chimiques dont ces poisons :



SUBSTANCES CANCÉROGENES CONNUES

INFORMATIONS PRÉSENTÉES PAR :

UNION EUROPÉENNE DES NON-FUMEURS - UEN
EUROPEAN UNION OF NON-SMOKERS
La défense des droits des non-fumeurs
"The defence of non-smokers' rights"

14, bd de Strasbourg F 67000 STRASBOURG

CONFÉDÉRATION FRANÇAISE DES TRAVAILLEURS CHRÉTIENS
La Vie à l'Échelle

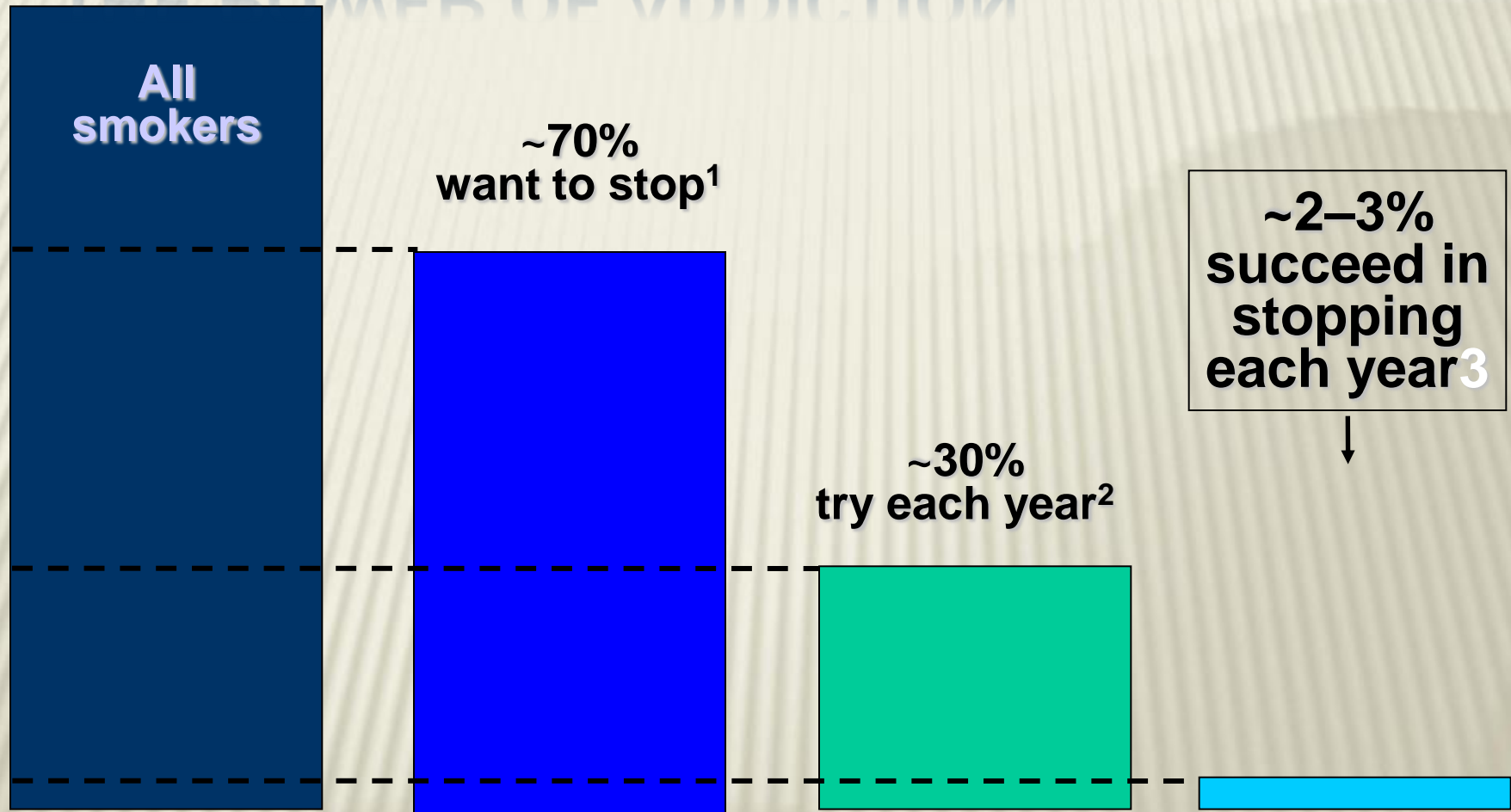
11, rue des Écluses Saint-Martin F 75013 PARIS

Project: Non-Smokers' Rights and Cancer Society of New Zealand
by: Anti-Smoking Foundation, Cancer Society

NICOTINE IS POWERFULLY ADDICTIVE

- Nicotine is as addictive as heroin or cocaine
- Nicotine addiction has a neurobiological basis
- 97% smokers fail to give up using willpower alone

THE POWER OF ADDICTION



1. Bridgwood *et al*, General Household Survey 1998. 2. West, *Getting serious about stopping smoking* 1997. 3. Arnsten, *Prim Psychiatry* 1996.

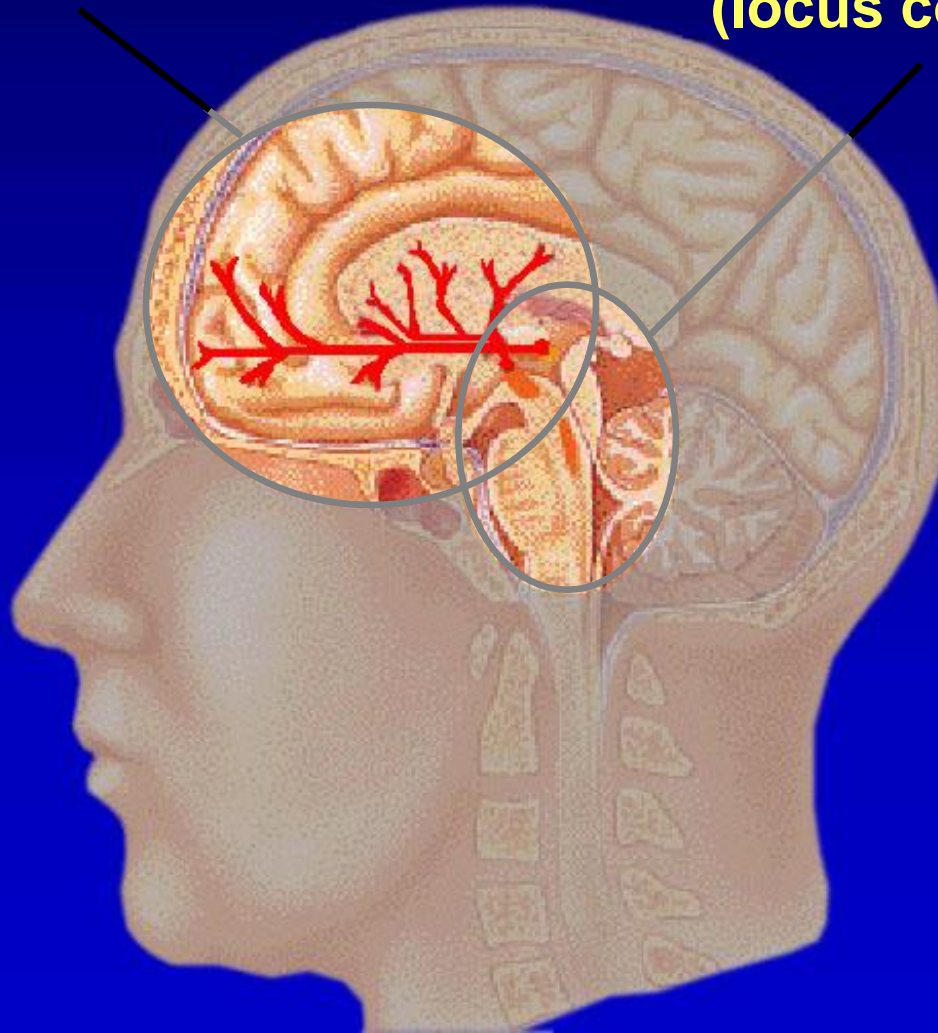
ICD

- ✖ Smoking is a disease, classified as mental and behavioural disorder due to use of tobacco F17.25
- ✖ *International Statistical Classification of Diseases and Related Health Problems, WHO 1992*

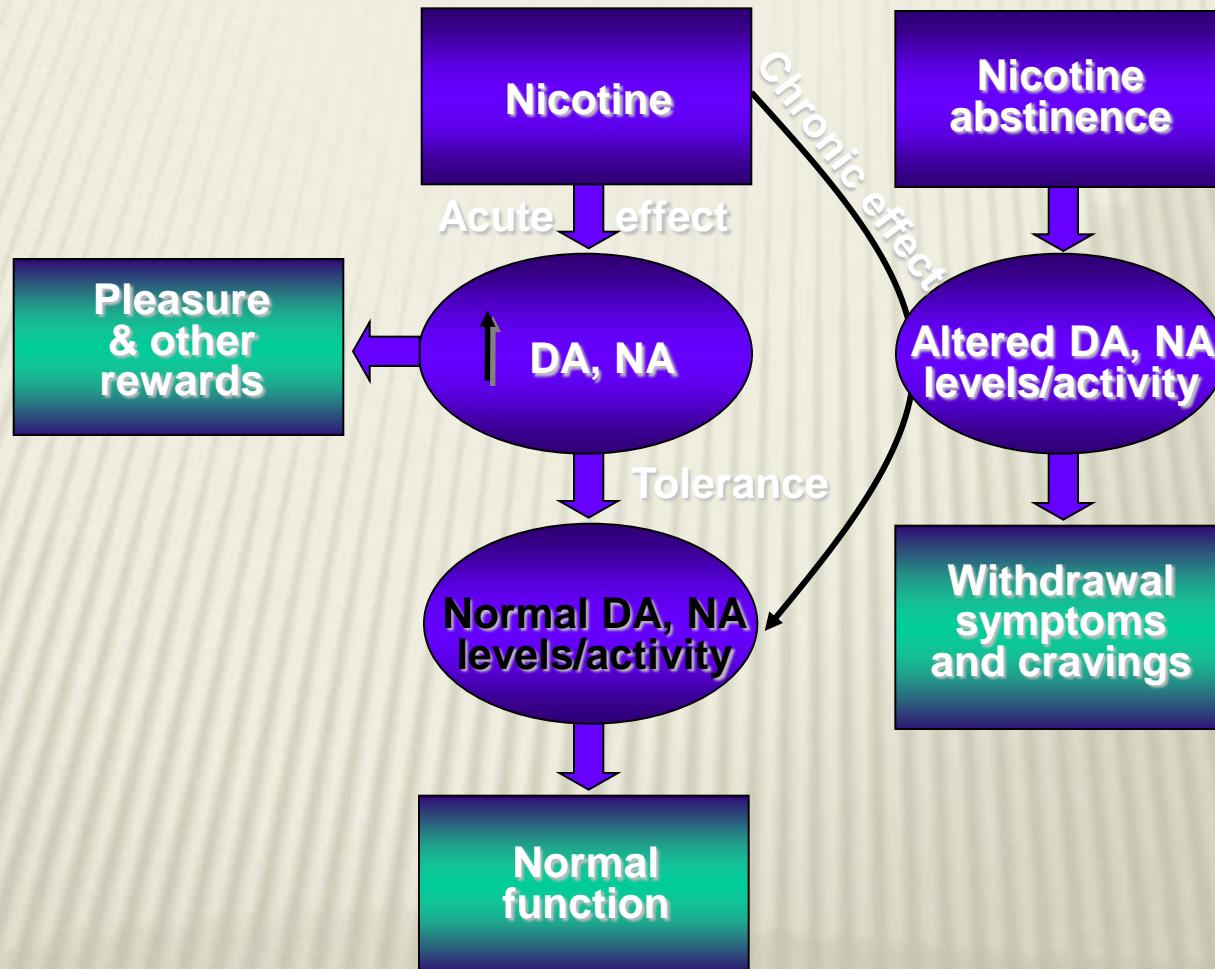
The addiction pathways

**'Reward' pathway
(mesolimbic dopamine system)**

**'Withdrawal' pathway
(locus coeruleus)**

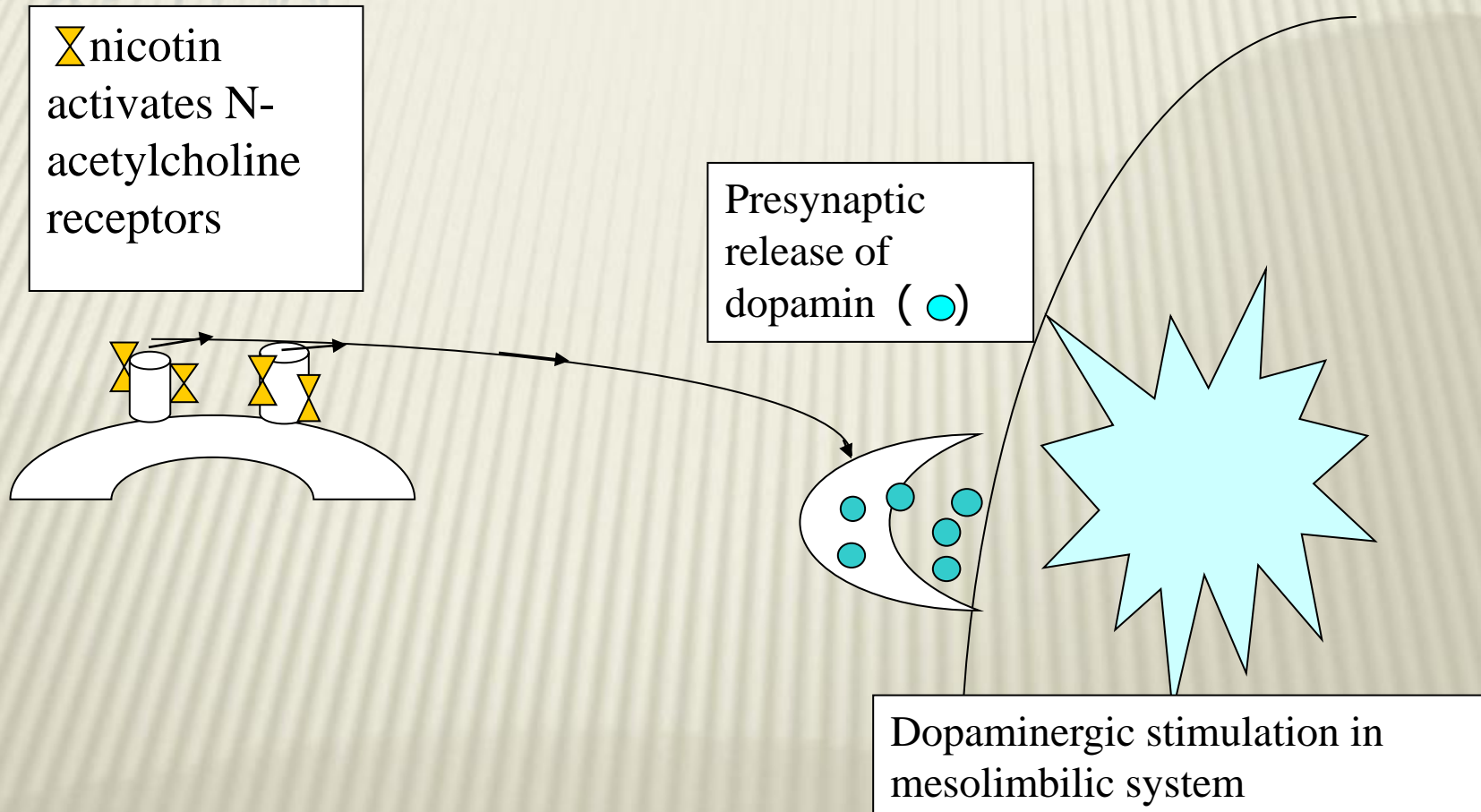


MECHANISMS OF ADDICTION



Key: DA = dopamine NA = noradrenaline

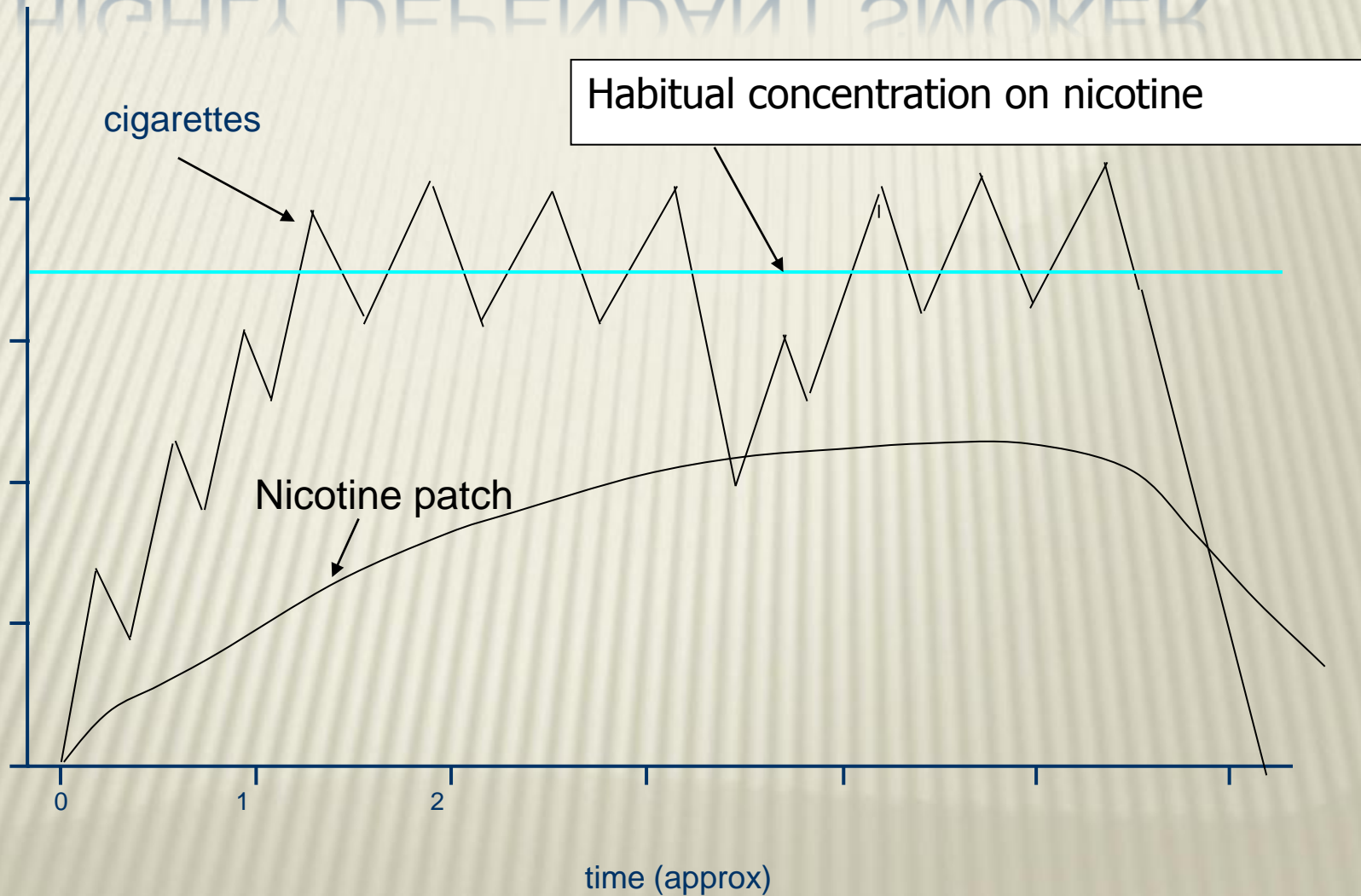
NEUROBIOLOGIC STIMULUS BY NICOTINE IN CENTRAL NERVOUS SYSTEM



COUNSELLING INCLUDES THE KNOWLEDGE OF NEUROBIOLOGIC ADDICTION

- ✘ Many smokers are thinking about smoking as a way of living and believe that it is only a habit
- ✘ A smoker feels euphoric directly after smoking a cigarette due to the neurobiologic stimulus of nicotine (“pipe of peace”)

DESIRABLE LEVEL OF NICOTINE FOR A HIGHLY DEPENDANT SMOKER



PHARMACOLOGICAL INTERVENTION

- Duration: 4-12 weeks (depends on severity of nicotine dependence)
- Nicotine replacement therapy (NRT)
 - patches
 - chewing gum
 - spray
- Bupropion (on prescription)
- Varenicline (on prescription)

NICOTINE REPLACEMENT THERAPY

- Based on nicotine weaning
- Increases chance of stopping by 1.6–2.3 fold¹
- Smokers try different formulations
- Different formulations have similar efficacy¹

1. Silagy *et al*, *The Cochrane Library* 1999.

FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE

- | | |
|--|--|
| ✖ How soon after you wake up do you smoke your first cigarette? | ✖ within 5 minutes (3 points) |
| | ✖ 5 to 30 minutes (2 points) |
| | ✖ 31 to 60 minutes (1 point) |
| | ✖ after 60 minutes (0 points) |
| ✖ Do you find it difficult not to smoke in places where you shouldn't (in church, school, movie, at library, on bus, in court, hospital)? | ✖ Yes (1 point) |
| | ✖ No (0 points) |
| ✖ Which cigarette would you most hate to give up; which cigarette do you treasure the most? | ✖ The first one in the morning (1 point) |
| | ✖ Any other (0 points) |
| ✖ How many cigarettes do You smoke each day? | |
| | ✖ 10 or fewer (0 points) |
| | ✖ 11 to 20 (1 point) |
| | ✖ 21 to 30 (2 points) |
| | ✖ 31 or more (3 points) |
| ✖ Do you smoke more during the first few hours after waking up than during the rest of the day? | ✖ Yes (1 point) |
| | ✖ No (0 points) |
| ✖ Do you still smoke if you are so sick that you are in bed most of the day, or if you have a cold or the flue and have trouble breathing? | ✖ Yes (1 point) |
| | ✖ No (0 points) |

NICOTINE REPLACEMENT THERAPY

3-4 weeks

3-4 weeks

3-4 weeks

15 mg

10 mg

5 mg

- Severe addiction (10...6)

- moderate (5...4)

- mild (3...0)

10 mg

5 mg

(5 mg)

THE EMOTIONAL STATE QUESTIONNAIRE (EST-Q-2)

- × To select the quitters with major depressive episode or anxiety
- × indicate how often each problem has bothered **during the past month**
- × Contains subscales of Depression, Anxiety,
- × Agoraphobia-Panic, Fatigue and Insomnia,

Subscale of depression (cut-point >12)

	Not at all	Seldom	Some- times	Often	All the time
Feelings of sadness	0	1	2	3	4
Feeling no interest in things	0	1	2	3	4
Feelings of worthlessness	0	1	2	3	4
Self-accusations	0	1	2	3	4
Recurrent thoughts of death or suicide	0	1	2	3	4
Feeling lonely	0	1	2	3	4
Hopelessness about the future	0	1	2	3	4
Impossible to enjoy things	0	1	2	3	4

Subscale of anxiety (cut-point >12)

	Not at all	Seldom	Some- times	Often	All the time
Feeling easily irritated or annoyed	0	1	2	3	4
Feeling anxious or fearful	0	1	2	3	4
Tension or inability to relax	0	1	2	3	4
Excessive worry about several different things	0	1	2	3	4
Feeling so restless that it is hard to sit still	0	1	2	3	4
Easily startled	0	1	2	3	4

BUPROPION SR

(ZYBAN/ELONTRIL/WELLBUTRIN)

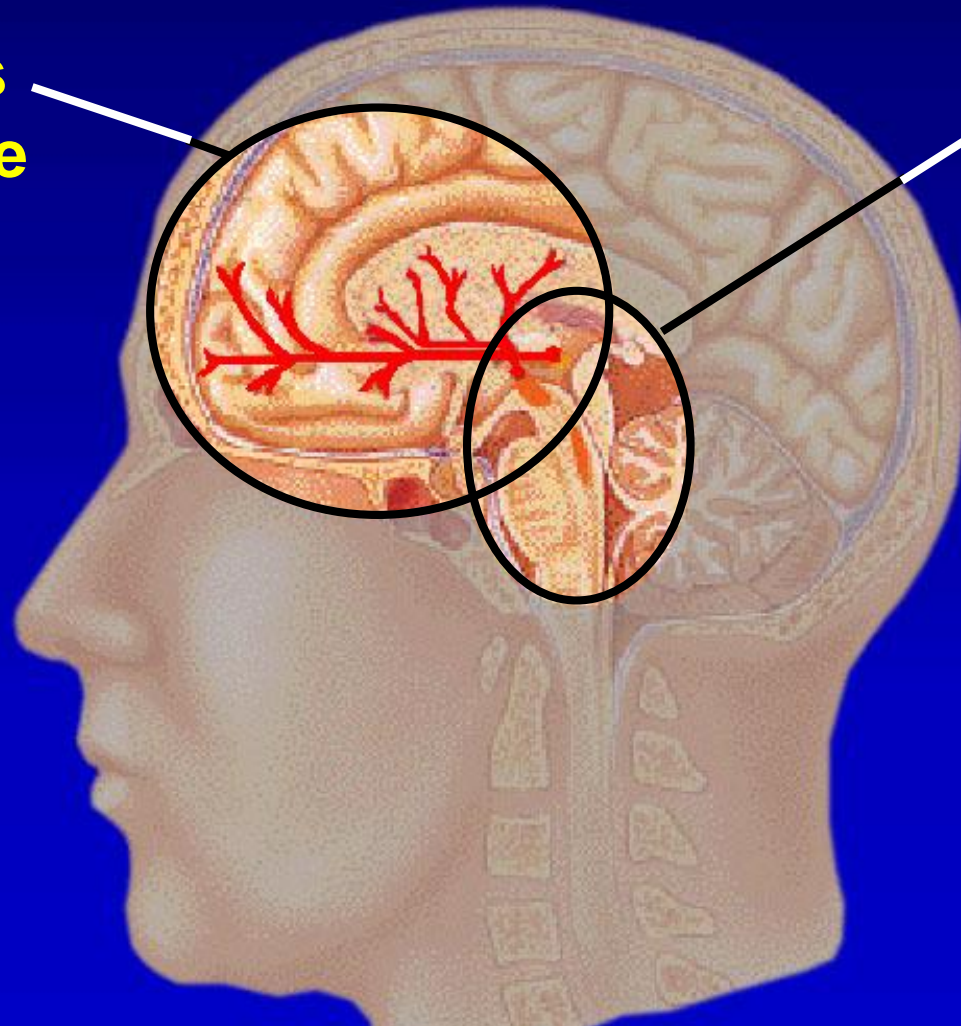
- Noradrenergic and dopaminergic properties
- inhibit the neuronal transports for dopamine and noradrenaline
- potentiates their effects in the brain
- an effective aid to smoking cessation

Ascher et al. Clin Psychiatry 1995
Martin et al. Psychopharmacology 1990
Goldstein. J Clin Psychiatry 1998
Hurt et al. N Engl J Med 1997

Bupropion HCl SR acts on the neurotransmitters involved in nicotine addiction

**Modifies
dopamine
release**

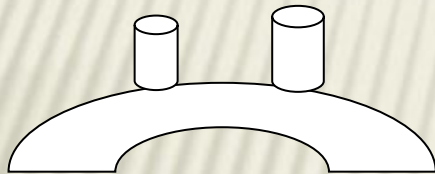
in 'reward'
pathway
(mesolimbic
system)



**Alters
noradrenergic
activity**

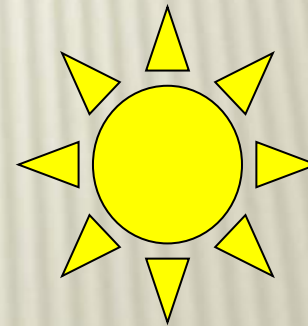
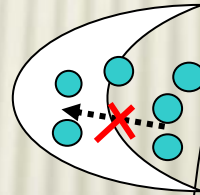
in 'withdrawal'
pathway
(locus coeruleus)

BUPROPIOONI TOIME KESKNÄRVISÜSTEEMIS



Nikotiini vajadus puudub
**Nikotiini vajadus
puudub**

Bupropioon päsib
dopamiini (●) tagasihaaret presünapsisse



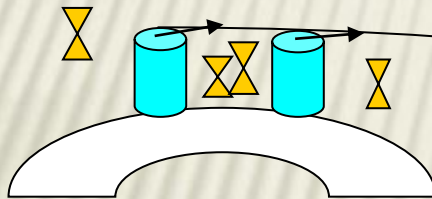
Dopamiinergiline stimulatsioon
mesolimbilises süsteemis

VARENICLINE (CHAMPIX)

- × Varenicline binds with high affinity and selectivity at the $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptor, where it acts as a partial agonist. Its binding both alleviates symptoms of craving and withdrawal, and reduces the rewarding and reinforcing effects of smoking by preventing nicotine binding to $\alpha 4\beta 2$ receptors.

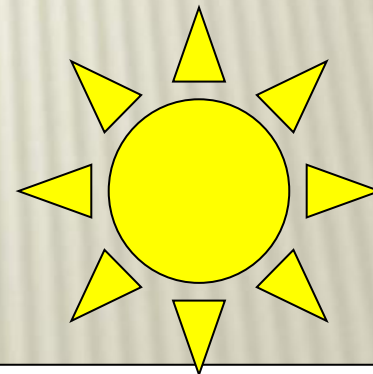
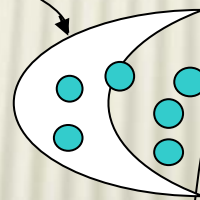
VARENIKLIINI TOIME KESKNÄRVISÜSTEEMIS

Varenikliin aktiveerib
N-atsetüülkoliini
retseptorid, samas
blokeerib retseptori
lisanikotiinile



 Nikotiini
molekulid ei
saa
aktiveerida
retseptoreid

Presünapsist
vabaneb
dopamiin (○)



Dopamiinergiline stimulatsioon
mesolimbilises süsteemis

BUPROPION OR VARENICLINE

- first 3 days 1 tab. x 1 + smoking
- next 4 days 1 tab. x 2 + smoking
- from the 8th day 1 tab. x 2 and quit smoking
- treatment will last for 7...8 weeks (12 weeks if needed)

DSM-IV DIAGNOSTIC CRITERIA FOR NICOTINE WITHDRAWAL

- Dysphoric or depressed mood
- insomnia
- irritability, frustration or anger
- anxiety
- difficulty concentrating
- restlessness
- decreased heart rate
- increased appetite or weight gain

NIKOTIINSÖLTUVUSE JA RAVI HINNAD (EUR)

	2 näd.	6 näd.	Kokku (8näd)
Näts “Nicorette” 20x/päevas	60	634	ca 694
16 t plaaster “Nicorette”	30	90	ca 120
24 t plaaster “Niquitin”	31	95	ca 126
Bupropion (F17)	23	72	ca 95
(F32 sood.50%)	13	59	ca 72
Varenikliin “Champix” (F17)	40	90	ca 130
Sigaretid 2.10/pakk (20sigaretti/päevas)	29.40	88.20	117.60 jätkub → 766/aastas

PROCESS OF QUITTING

