



# Nicotine replacement therapy

Dr Munir Abu-Helalah  
Associate Professor of Epidemiology  
and Preventive Medicine

Why is it difficult for smokers to quit smoking? Nicotine addiction.

People will start 1 cigarette  $\rightarrow$  2  $\rightarrow$  3+

$\hookrightarrow$  and this will cause increase of the expression of  $\alpha/B$  receptor, and with time people will have tolerance to nicotine.

smoke  $\rightarrow$   $\uparrow$  dopamine  $\rightarrow$  euphoria + excitement + enjoyment  $\rightarrow$  after a while nicotine  $\downarrow$   $\rightarrow$  dopamine  $\downarrow$   $\rightarrow$  crave for another cigarette.

Tobacco addiction = dopamine release

$\hookrightarrow$  nicotine enter to brain and stimulate  $\hookrightarrow$

Dopamine:  $\uparrow$  performance, happiness, ...

Dopamine  $\downarrow$  (smokers): anxiety, depression, difficulty in concen., insomnia

\* To help smokers quit smoking we need either to provide nicotine to replace the withdrawal symptoms or block these receptors.

لما الشخص يوقف التدخين ← تظهر عليه أعراض الانسحاب والتأرق و، والتزعاج ←

وعادةً أيتها ٢٤ - ٤٨ ساعة (critical period) ولو الشخص تجاوزها بقدر يتترك

التدخين بسهولة ← مكانه في علاج يعطى ٨ - ١٢ أسبوعاً مكانه أنأكد ما يرجع

مرة ثانية و الكافين كلها تترواح تماماً.

<sup>٢٤</sup> withdrawal symptoms of smoking: أعراض انسحابية لتترك التدخين

کثیر فی امران نسیح استخوان عظم سرطان + امراض قلب + COPD ولسا بخیرا ← دوا  
الناس سے یہ نیکروا، انہ ترک، لیکن رجیکر علی لانی بہ ←

*It's never too late to quit smoking*

If you stop at a point with ischemic  $\heartsuit$  disease we can  $\downarrow$  the risk by 25%  
of recurrent MI.

وین حتی لو مرض مجرد بانہ ترک، لیکن اینا رجیکر علی لانی، مرض الحکم +  
complication relab.

when we start giving treatment/replacement or therapy to smokers  
they will notice something after 62 hrs they will feel that

it's easy to quit smoking → after month they will look diff.  
(skin appearance) → after 3-9 months cough ↓, breathing rate will be better.

After 1 year, these smokers will have  $\frac{1}{2}$  the risk of non smokers,

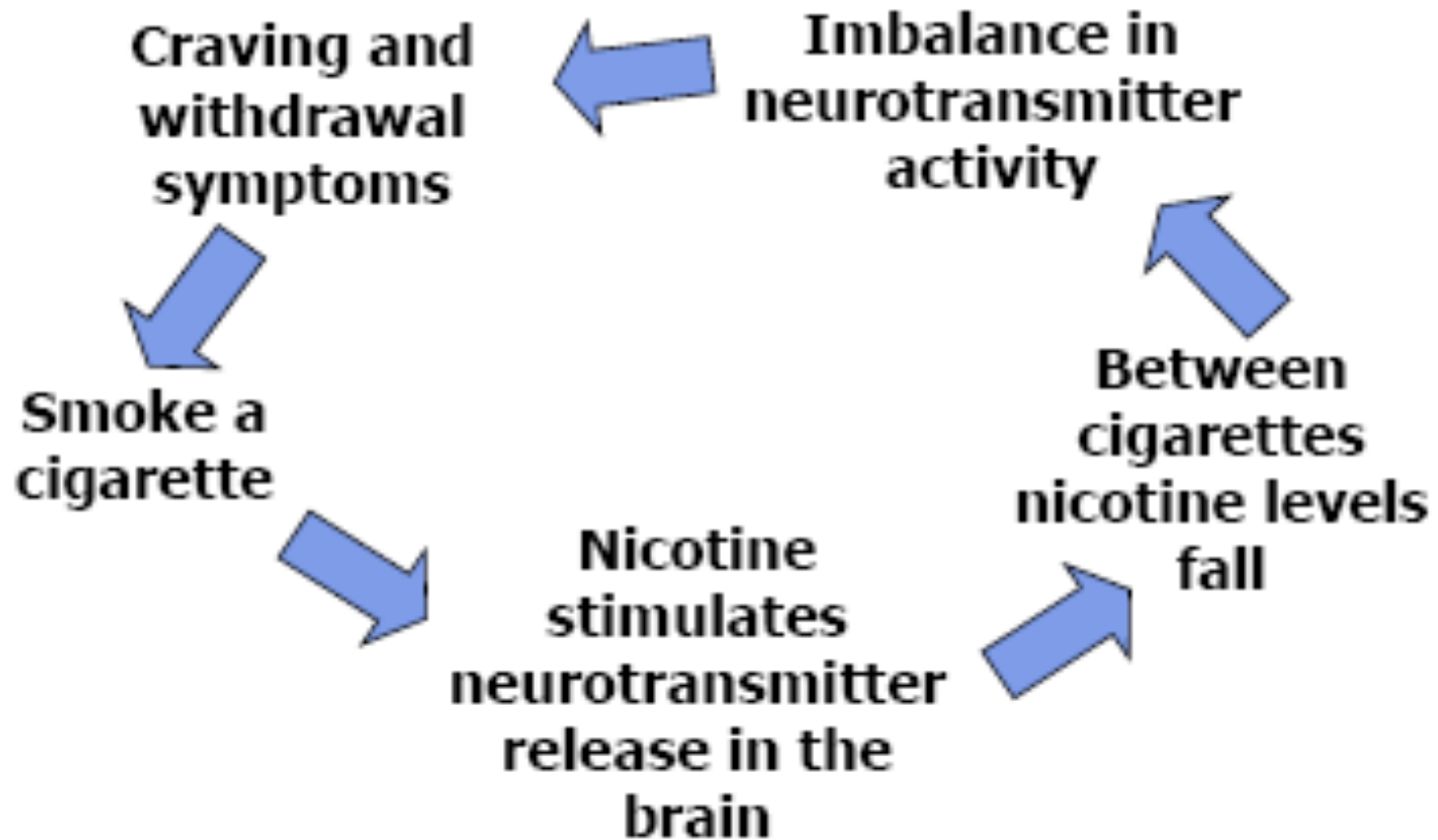
After 10 years, the risk of MI will be the same for people who had never smoked

إذا درستوا هذه notes فانهم سوف يسهلوا (سبب ترفيقي).

# Addiction to nicotine

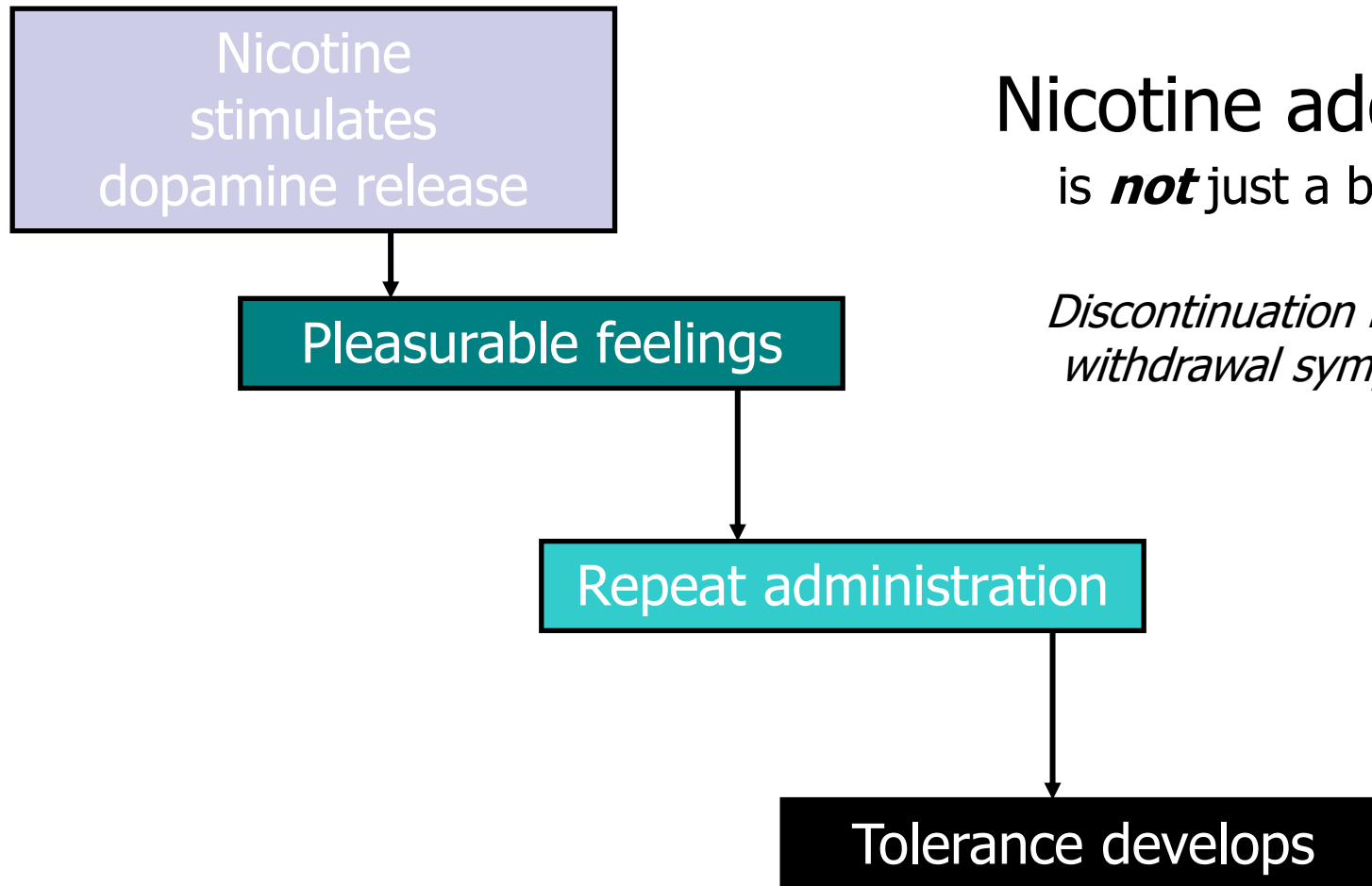
- An understanding of how nicotine produces addiction and influences smoking behavior provides a necessary basis for smoking cessation therapies.
- Chronic nicotine exposure results in neuroadaptation, that is, the development of tolerance.
- Neuroadaptation is associated with an increased number of brain nicotinic cholinergic receptors.
- Chronic exposure to nicotine also results in changes in gene expression and neural plasticity; which is defined as “ability of the brain to reorganize neural pathways based on new experiences”

# Nicotine Addiction



Kauer, J.A. & Malenka, R.C. Synaptic plasticity and addiction. *Nat. Rev. Neurosci.* 8, 844–858 (2007).

# BIOLOGY of NICOTINE ADDICTION: ROLE of DOPAMINE



Nicotine addiction  
is ***not*** just a bad habit.

*Discontinuation leads to  
withdrawal symptoms.*



# DOPAMINE REWARD PATHWAY

Prefrontal cortex

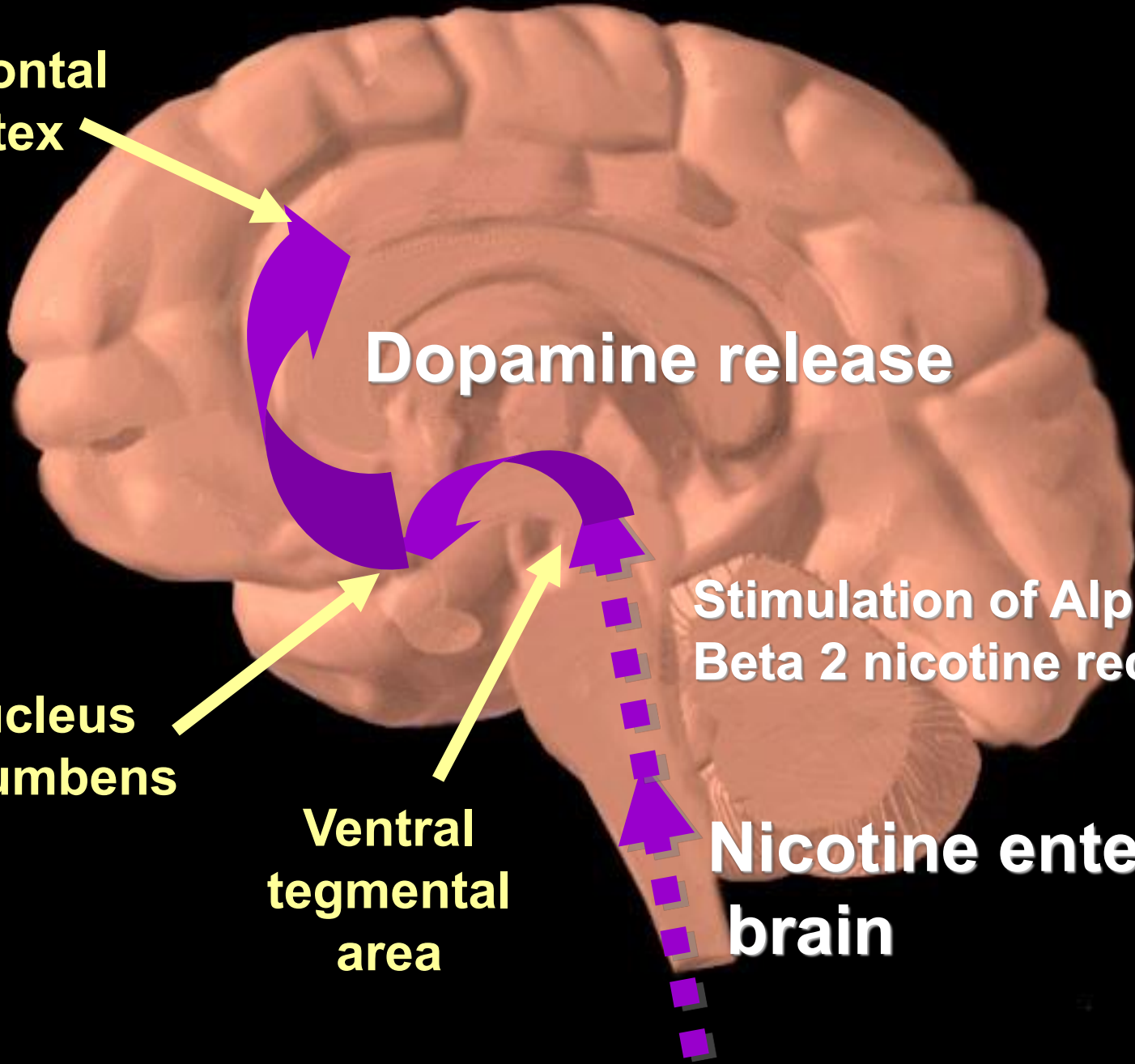
Dopamine release

Nucleus accumbens

Ventral tegmental area

Stimulation of Alpha 4 Beta 2 nicotine receptors

Nicotine enters brain



# Dopamine

- **Dopamine induces feelings of euphoria and pleasure and is responsible for activating the dopamine reward pathway**
- The dopamine reward pathway, as depicted in this simplified diagram, is a network of nervous tissue in the middle of the brain that elicits feelings of pleasure in response to certain stimuli.

# Addiction to nicotine

- **Addiction to tobacco is multifactorial:**
- It includes a desire for the direct pharmacologic actions of nicotine, relief of withdrawal symptoms, and learned associations.
- Smokers usually provide different reasons for smoking that could include pleasure, arousal, enhanced vigilance, improved performance, relief of anxiety or depression, reduced hunger, and control of body weight

# Addiction to nicotine

- The absence of nicotine due to smoking cessation results in subnormal release of dopamine and other neurotransmitters.
- Nicotine withdrawal results in the state of deficient dopamine responses to novel stimuli in general and a state of malaise and inability to experience pleasure.
- This leads to development of nicotine withdrawal symptoms.

# NICOTINE PHARMACODYNAMICS: WITHDRAWAL EFFECTS

- Depression
- Insomnia
- Irritability/frustration/anger
- Anxiety
- Difficulty concentrating
- Restlessness
- Increased appetite/weight gain
- Decreased heart rate
- Cravings\*

Most symptoms  
peak 24–48 hr  
after quitting and  
subside within  
2–4 weeks.

## Timeline of health benefits after stopping smoking

<b>Time line (After ...)</b>	<b>Health Benefit</b>
<b>72 hours</b>	<b>Breathing becomes easier. Bronchial tubes begin to relax and energy levels increase.</b>
<b>1 month</b>	<b>Skin appearance improves, owing to improved skin perfusion.</b>
<b>3-9 months</b>	<b>Cough, wheezing, and breathing problems improve and lung function increases by up to 10%.</b>
<b>1 year</b>	<b>Risk of a heart attack falls to about half that of a smoker.</b>
<b>10 years</b>	<b>Risk of lung cancer falls to about half that of a smoker.</b>
<b>15 years</b>	<b>Risk of heart attack falls to the same level as someone who has never smoked.</b>

Source: <http://www.ash.org.uk/stopping-smoking/quitting-smoking>

# Management of smoking cessation

Behavioural therapy (tell someone if they're mad for example, to take a fresh breath instead of smoking) (DON'T HELP IN MANAGEMENT OF WITHDRAWAL SYNDROMES, it will help with the practice)

and

Nicotine replacement therapy

Or nicotine receptors antagonists

دكتور قال ان حضر مؤتمرو وكان في خلاف على نقطة اوله ونوع انه حاجة للزقات  
او الراجح و مجرد الاكتفاء بالقصوف لثلاث ايام اذا عصبته اوقف عن السجك او اذا بدى اذنه  
انسك امي يلهيني ونس قال ان خاطر و عيكة الاستغناء عن السجك .  
And based on clinical trials → i will see what protocol to use 11

\* Meta analysis: combination of clinical trials if you can't combine the trials together → systematic review

The strongest type of evidence meta analysis or systematic reviews  
↳ go back to the activity (mid exam)

followed by analytical studies.



# Nicotine replacement therapy

(NRT) (3rd step)

- Provides smoker with nicotine without using tobacco, thereby relieving nicotine withdrawal symptoms.
- NRT products differ in the route of delivering nicotine to the circulation.
- Nicotine is absorbed transdermally with the nicotine skin patch, through the nasal mucosa by the nasal spray, or through the oral mucosa with the nicotine chewing gum, nicotine lozenge, or nicotine inhaler + drops.
- Nicotine patches are more tolerated than nasal spray and provides the most continuous delivery of nicotine of nicotine replacement therapies.

(Based on evidence, we have ↑)

for an educated, cooperative patient → Patch + gum  
for low education, non cooperative → Patch + Varenicline  
بیمار آگاه و همکاری کننده → پاش + گام  
بیمار کم‌سواد و همکاری کننده → پاش + واریکلین

# Nicotine replacement therapy (NRT)

*Replace cigarette with nicotine*

## ■ Principle:

Many of the difficulties in smoking cessation stems from problems posed by nicotine withdrawal.

# Nicotine Replacement Therapy (NRT)

- Reliably attenuates severity of withdrawal, making it easier for would-be ex-smokers to cope with abstinence while unlearning the deeply ingrained habit elements of smoking

Spatch

Sgum

Lozenge drops  
↳ they're used when people have dental problems.

# Selected Medication Options: Monotherapy and Combination Therapy

Medication	Number of arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Nicotine Patch	32	1.9 (1.7 - 2.2)	23.4% (21.3 - 25.8)
Bupropion SR	26	2.0 (1.8 - 2.2)	24.2% (22.2 - 26.4)
Varenicline	5	3.1 (2.5 - 3.8)	33.2% (28.9 - 37.8)
Patch (>14 wks) + NRT (gum or spray)	3	3.6 (2.5 - 5.2)	36.5% (28.6 - 45.3)
Patch + Bupropion SR	3	2.5 (1.9 - 3.4)	28.9% (23.5 - 35.1)

## NRT - Therapeutic Effect

- The primary therapeutic effect of NRT is to reduce the severity of symptoms associated with smoking cessation.
- NRT provides steady levels of nicotine and may reduce the pleasurable effects of tobacco desired by smokers.
- NRT makes it easier to cope in difficult situations.

# Nicotine patches :

- Transdermal patch (waterproof)
- Nicotine Replacement Therapy (NRT) ← *third choice based on evidence*
- To overcome withdrawal symptoms
- 24-hour patch to deliver constant nicotine levels
- 12 week weaning program that reduces and eliminates body's dependence for nicotine
- Clinically-proven to be better than willpower alone
- 2-4 times the success rate of placebo patches

*combination therapy*

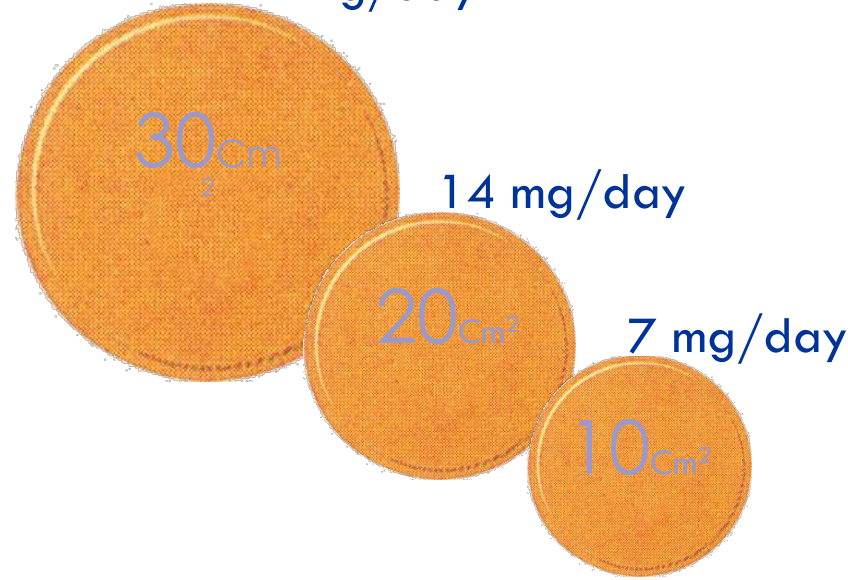
Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Arch Intern Med.* 1999;159:2033-2038.

# Nicotine patches

\* 21 or 24mg/<sup>1 week</sup>24hrs, 14mg/<sup>2 weeks</sup>24hrs, 7mg/<sup>2 weeks</sup>24hrs

\* 21 or 24mg/16hrs, 14mg/16hrs, 7mg/16hrs

\* 15mg/24hrs, 10mg/24hrs, 5mg/24hrs  
21 mg/day



off nicotine 8 hrs  
at night  
and wake up  
at the early morning  
for the next dose.

most programs are for 12 weeks 6 weeks 3 weeks 3 weeks  
or 8 weeks 2 weeks 2 weeks

انفوجہ کا سب سے زیادہ دیر تک استعمال کرنے والے لوگوں کے لیے بہترین ہے

# Precautions

- ❑ women who are pregnant or breast feeding
- ❑ smokers with cardiovascular conditions

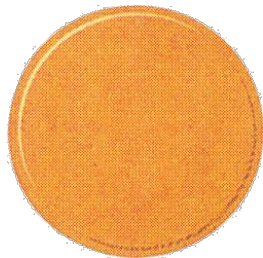
Doctors should weigh risks/vs benefits when prescribing NRT to pregnant women or smokers with cardiovascular conditions.

- ❑ smokers using other nicotine replacement products
- ❑ children
- ❑ non-smokers
- ❑ smokers of fewer than 10 cigarettes a day



# Nicotine patches– Application

- Apply to non-hairy, clean, dry skin
- Rotate between sites (this helps to reduce the risk of skin irritation)
- Choose a flat surface
- Avoid joints or skin folds
- Replace the same time everyday



**DO NOT SMOKE WHILE  
USING THE PATCH**

imp.  
if i didn't  
give up the right  
time, steady  
state level  
will not be  
maintained

# Why a 24-hour patch ?

▶ Many of the dependent smokers

○ Either smoke just before to go to bed,

○ Or wake up at night for smoking →

○ Or wake up early in the morning to have a cigarette

*[Night smoking is a criteria for strong addiction to nicotine]*

ما كان يفتقر إلى إيقاع 16hrs Patch

Patches have slow release of nicotine (sustained release)

↳ we combine it with gum or lozenge.

عندما نقرزمرة واحدة فإذا الشخص فجأة استمر أو عصب يلائي

↳ with immediate release

وهذا كمن أحسنه monotherapy و نسبة النجاح  
تزيد من ٢-٤ إلى ١٠ أضعاف

\* we need to be careful if we prescribed it for a breastfeeding  
or pregnant woman → we will advise her and she has the freedom  
of choice → والله اعلم، كواله يتكروا بحالهم

# Nicotine Lozenges *(immediate release)*

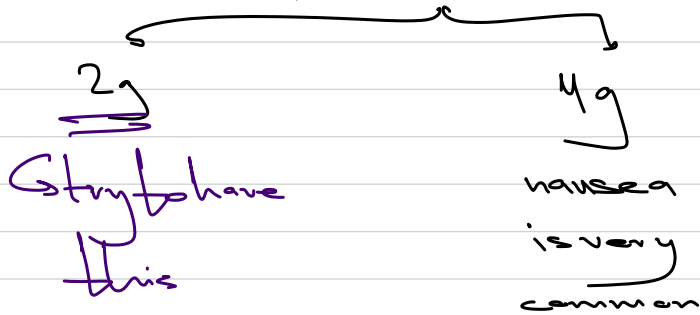
*(you should not smoke when you take)*

- Nicotine Lozenges are new products that have similar efficacy to nicotine gum but it is easier to use and does not require special technique for optimal use.
- It also delivers more nicotine than equivalent dose of the gum.
- Unlike nicotine gum, smokers with dentures or poor dentition can use Lozenges.

*\* It's preferable to use it with a P-tdh specially the first month*

\* We give it to patients with Ischemic  $\heartsuit$  disease when they refuse to give smoking.

\* we need to be careful we have 2 doses



# High level of smoking addiction

✿ Combination of behavioural therapy with nicotine patches and nicotine lozenges (used for cravings)

↳ smokers that cannot cope and say that they only w- f cigarettes

Or

✿ Combination of varenicline with behavioural therapy

# For patients with ischaemic heart disease with moderate or high level of addiction:

- The best approach is to start with **behavioural therapy**

If failed, you can start with nicotine patches <sup>or lozenges</sup>

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نیکوٹین گام و پاتھ کا استعمال سے احتیاط، لہذا!

↓  
nicotine poisoning

so we advice them to take ↓

# Varenicline (Champix, Chantix)

- a partial agonist at the alpha4beta2 subunit of the nicotinic acetylcholine receptor.
- This drug binds to nicotinic receptors leading to reduction of withdrawal symptoms and decrease rate of cigarettes' nicotine binding to these receptors.

*Compared with patch, patch & gum are superior*



# Varenicline (Champix, Chantix)

- This medication has shown a good abstinence rate when compared to nicotine patches, but the difference is small when compared to combined nicotine patches with gum or lozenges.

# Varenicline (Chantix, Chantix)

- Week 1: Starting dose: 0.5mg once daily for three days, then 0.5mg twice daily for four days. *(when you block the receptors of the brain, you won't have any desire to smoke)*

Smokers have to decide on quit day during this week.

- Then

1mg twice daily for 8-12 weeks.

*main meal* إذا كان عرسه  
أخيه *nausea*: سببها الدوا  
باليوم ← فيفكروا به + كذا

# Contraindications

- Varenicline has not been studied in children and should not be taken by young people who are under 18 years of age.
- Breast feeding. Varenicline may pass into breast milk.

Either use an alternative therapy or follow other ways of feeding the baby may be appropriate if she is currently taking the drug.

## Precautions for varenicline use

*\* chronic diabetic patients or patients with hypertension, you should check*

- ✓ ■ kidney problems or on dialysis. It may be appropriate for prescribe a lower dose.
- Pregnancy. The effects of Varenicline on the foetus are not known and it would be better if the lady quits smoking before getting pregnant.
- ■ Depression or any psychiatric illnesses in the past.

# Varenicline: Side effects

- Vomiting and nausea
- Headaches
- Sleep disturbances and atypical dreams
- Gas (wind)
- Changes in the way food tastes (Dysgeusia)
- Constipation
- **Suicidal thoughts**

↳ and many of them committed suicide +

اكتشفوا انهم لم يكونوا من المحبطين  
نفسية + اكتئاب في ماضيهم شأنه انهم  
انهم لم يكونوا المحبطين

# Bupropion (Zyban)

*Strengthened for Depression*

- Available as an antidepressant in the United States since 1989, is believed to act by enhancing central nervous system noradrenergic and dopaminergic release.
- A sustained-release formulation of the drug is licensed as an aid to smoking cessation (Zyban); it is identical to the antidepressant Wellbutrin SR and is available as a generic drug.

\* Zylan was observed to stop smoking when  
physicians prescribed it as an antidepressant  
and they then noticed how it made many  
patients stop smoking

و هو سيء الفتح وإذا كان في الكتاب هذا يدل على كماله  
مرة واحدة.

# Bupropion (Zyban) *(twice daily)*

- **Safety** — The most common side effects of bupropion are **insomnia, agitation, dry mouth, and headache.**
- A more serious side effect is **seizure**, which can occur because bupropion reduces the seizure threshold.
- In clinical trials, the risk of seizure was 0.1 percent, and **the drug is contraindicated in patients with a seizure disorder or predisposition to seizure.**



1. 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)
2. Do you find it difficult not to smoke in places where you shouldn't, such as in church or school, in a movie, at the library, on a bus, in court or in a hospital?
  - Yes (1 point)
  - No (0 points)
3. 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 one (0 points)
4. 4. 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)
5. 5. 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)
6. 6. 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 flu and have trouble breathing?
  - Yes (1 point)
  - No (0 points)

**Scoring:** 7–10 points = highly dependent; 4–6 points = moderately dependent; less than 4 points = minimally dependent.