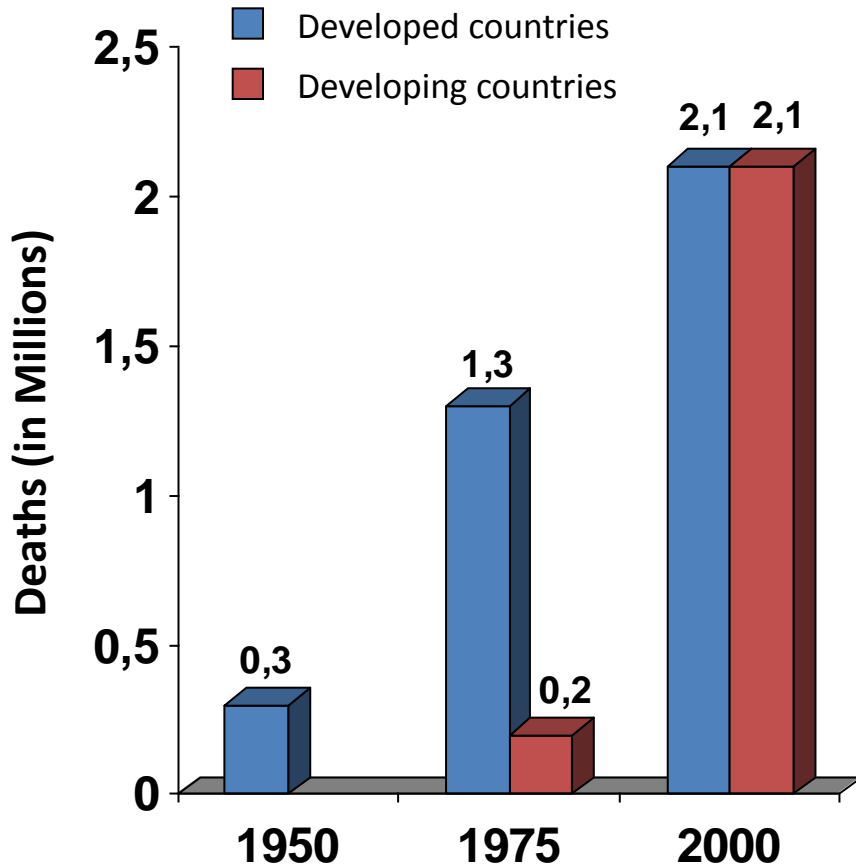


Κατευθυντήριες οδηγίες στην Διακοπή του Καπνίσματος

*Ι. Μητρούσκα
Πνευμονολόγος
ΠΑΓΝΗ Κρήτη*

Why to treat tobacco use

Deaths Attributable to Tobacco¹



- Tobacco kills up to half of its users.
- Tobacco kills nearly 6 million people each year.
 - More than five million of those deaths are the result of direct tobacco use while more than 600 000 are the result of non-smokers being exposed to second-hand smoke.
- Unless urgent action is taken, the annual death toll could rise to more than eight million by 2030.
- Nearly 80% of the world's one billion smokers live in low- and middle-income countries

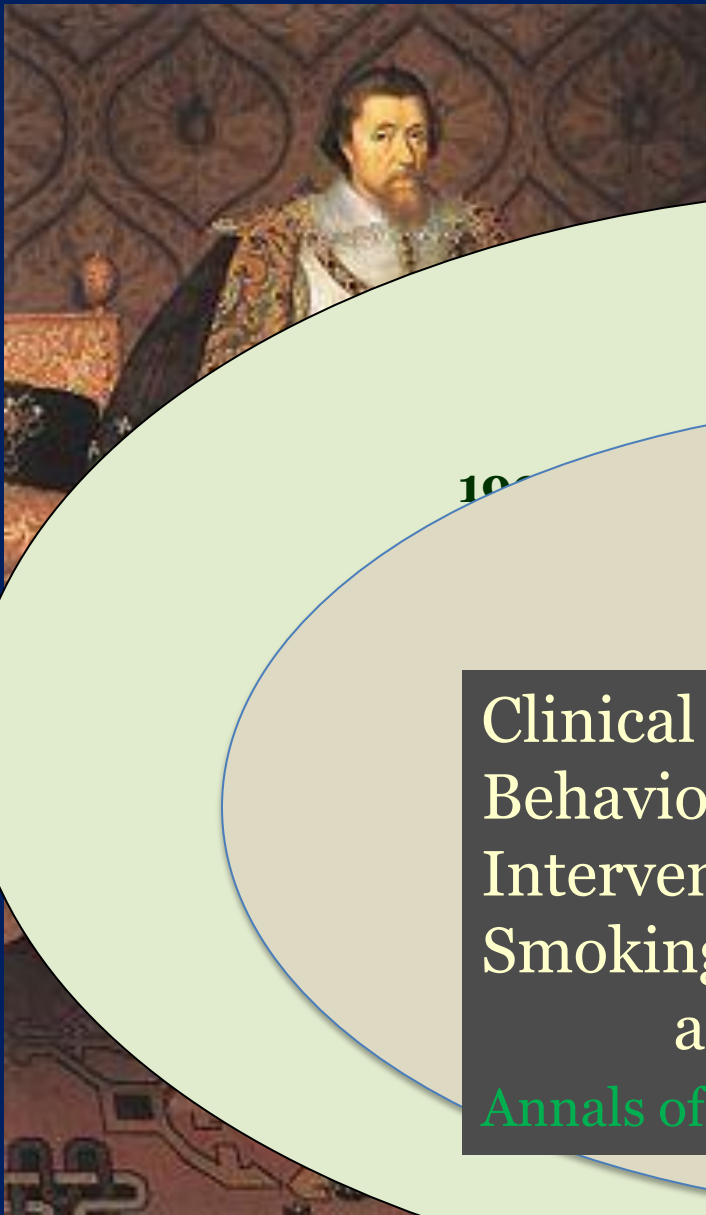
1. Mackay J, Eriksen M. *The Tobacco Atlas*. Geneva, Switzerland WHO; 2002,

2. *International treaty for tobacco control*. WHO; 2014

Intervention ^b	Affordability			
	Low-income (Nepal)	Lower-middle-income (India)	Upper-middle-income (China)	High-income (UK)
Automated text messaging	7.7	11.2	25.9	109.5
Brief health-worker advice	2.7	7.8	18.0	12.3
Printed self-help materials	2.4	4.6	10.8	19.3
Cytisine	1.7	4.9	11.3	15.0
Nortriptyline	1.4	4.1	9.5	8.6
Proactive telephone support	1.0	3.8	9.7	4.5
Face-to-face behavioural support ^c	0.9	3.4	8.6	4.0
Bupropion	0.5	1.6	3.7	7.7
Varenicline	0.5	1.3	3.0	9.2
NRT (single) ^d	0.4	1.0	2.4	6.9

West R Addiction 2015

History



...ed to smoking as:
...he sin

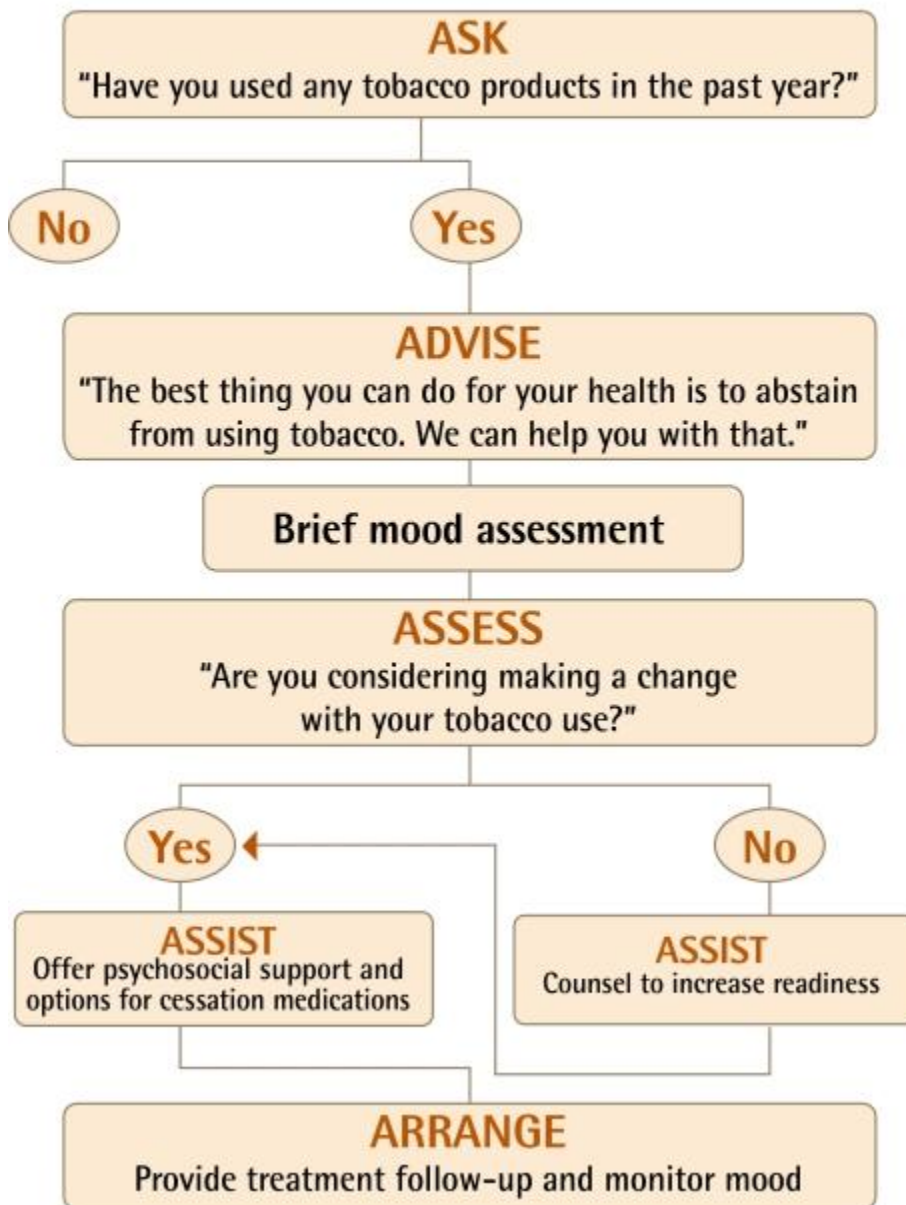
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2015

Clinical Guidelines
Behavioral and Pharmacotherapy
Interventions for Tobacco
Smoking Cessation in Adults
and Pregnant women

Annals of Internal Medicine



Θεραπεία της εξάρτησης από
την νικοτίνη

—

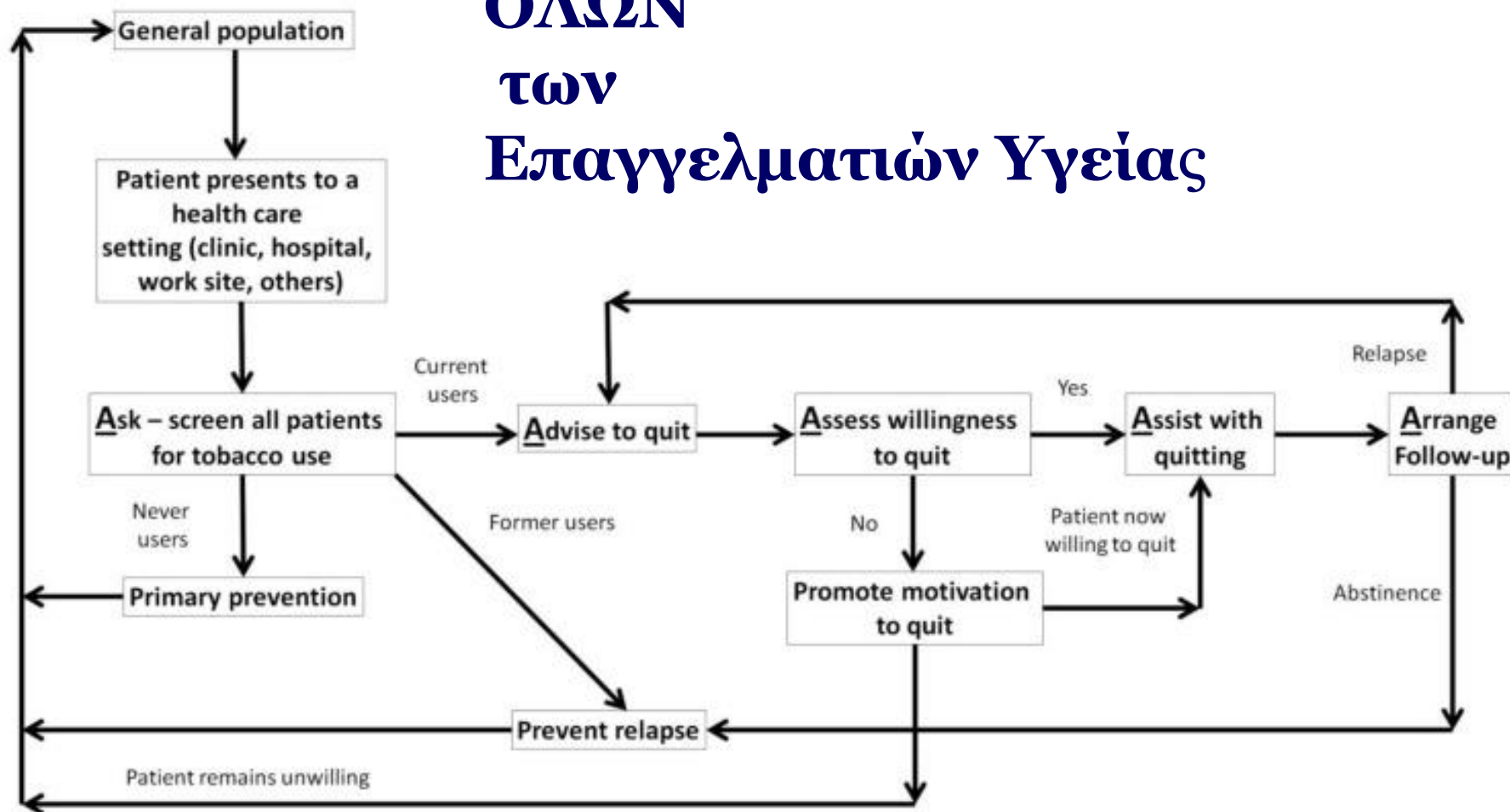
μια συνεχόμενη φροντίδα

Can Fam Physician. 2011; 57(6):647–649.

Population	Nonpregnant adults aged ≥18 y	Pregnant women aged ≥18 y	Pregnant women aged ≥18 y	All adults aged ≥18 y
Recommendation	Provide pharmacotherapy and behavioral interventions for cessation. Grade: A	Provide behavioral interventions for cessation. Grade: A	Pharmacotherapy interventions: No recommendation. Grade: I statement	ENDS: No recommendation. Grade: I statement

Assessment	<div>Τα 5 Α αποτελούν μια χρήσιμη στρατηγική εμπλοκής των ασθενών στην συζήτηση της διακοπής του καπνίσματος</div>			
Behavioral Counseling Interventions	... and self-help materials) or combined with pharmacotherapy substantially improve achievement of tobacco cessation.	... smoking abstinence, increase infant birthweight, and reduce risk for preterm birth.		
Pharmacotherapy Interventions	Pharmacotherapy interventions, including NRT, bupropion SR, and varenicline—with or without behavioral counseling interventions—substantially improve achievement of tobacco cessation.		There is inadequate or no evidence on the benefits of NRT, bupropion SR, or varenicline to achieve tobacco cessation in pregnant women or improve perinatal outcomes in infants.	There is inadequate evidence on the benefit of ENDS to achieve tobacco cessation in adults or improve perinatal outcomes in infants.
Balance of Benefits and Harms	The USPSTF concludes with high certainty that the net benefit of behavioral interventions and FDA-approved pharmacotherapy for tobacco cessation, alone or in combination, is substantial.	The USPSTF concludes with high certainty that the net benefit of behavioral interventions for tobacco cessation on perinatal outcomes and smoking abstinence is substantial.	The USPSTF concludes that the evidence on pharmacotherapy interventions for tobacco cessation is insufficient because of a lack of studies, and the balance of benefits and harms cannot be determined.	The USPSTF concludes that the evidence on the use of ENDS for tobacco cessation is insufficient, and the balance of benefits and harms cannot be determined.
Other Relevant USPSTF Recommendations	The USPSTF recommends that primary care clinicians provide interventions, including education or brief counseling, to prevent the initiation of tobacco use in school-aged children and adolescents. This recommendation is available on the USPSTF Web site (www.uspreventiveservicestaskforce.org).			

Γενική στάση απέναντι στο κάπνισμα ΟΛΩΝ των Επαγγελματιών Υγείας



Adapted from: Fiore MC, Jaen CR, Baker TB *et al.* Treating Tobacco Use and Dependence: 2008 Update. U.S. Department of Health and Human Services 2008. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK63952/>.

ASK

Ask all patients

Do you still smoke tobacco?

- Record smoking status (current smoker)

Yes

Assess

- Assess stage of change: 'How do you feel about your smoking at the moment?' and 'Are you ready to stop smoking now?'
- Record stage of change
- Assess nicotine dependence

Advise

All smokers should be advised to quit in a way that is clear but nonconfrontational eg. 'The best thing you can do for your health is to quit smoking'

No

Ask all patients

Check every 5 years, or more frequently if under 25 year of age or an ex-smoker

Yes

- Affirm decision to quit and record smoking status (ex-smoker)
- Give relapse prevention advice if quit <1 year
- Ongoing encouragement up to at least 5 years quit

No

- Affirm choice not to smoke and record smoking status (never smoker)

Assess nicotine dependence

- Nicotine dependence

1. 'How

a

- Pharmacological treatment increases the chances of successfully quitting

Υπολογισμός
εξάρτησης από την
νικοτίνη

ASSESS

ADVISE

Προσδιορισμός βαθμού εξάρτησης

Ποιοτικές μέθοδοι

- Η απλούστερη ποιοτική προσέγγιση αφορά σε ερωτήσεις του τύπου:
 - *Το βρίσκετε δύσκολο να μην καπνίζεται σε καταστάσεις που φυσιολογικά καπνίζετε;*
 - *Προσπαθήσατε στο παρελθόν να διακόψετε το κάπνισμα οριστικά αλλά διαπιστώσατε ότι δεν μπορείτε;*

Προσδιορισμός βαθμού εξάρτησης

Ποσοτικές μέθοδοι

- Fagerstrom test:
 - Είναι η συχνότερα χρησιμοποιούμενη μέθοδος
 - Έχει αποδειχθεί χρήσιμη στην πρόβλεψη της εξέλιξης της προσπάθειας διακοπής
 - Όσο μεγαλύτερη η βαθμολογία τόσο μεγαλύτερη η εξάρτηση
 - Η ερωτήσεις που αφορούν στον αριθμό των τσιγάρων / 24ωρο και στην ώρα του πρώτου τσιγάρου έχουν την μεγαλύτερη προγνωστική αξία

Fagerstrom Test for Nicotine Dependence (FTDN)

Ερώτηση	Responses	Scores
1. Σε πόση ώρα αφού ξυπνήσετε ανάβετε το πρώτο σας τσιγάρο;	Within 5 minutes 6 – 30 minutes 31 – 60 minutes After 60 minutes	3 2 1 0
2. Το βρίσκετε δύσκολο να μην καπνίζετε σε χώρους που απαγορεύεται το κάπνισμα; (e.g. in the cinema, at meetings etc)	Yes No	1 0
3. Ποιο τσιγάρο (στη διάρκεια της μέρας) σας είναι πιο απαραίτητο;	The first in the morning Any other	1 0
4. Πόσα τσιγάρα καπνίζετε την ημέρα ;	10 or less 11 – 20 21 – 30 31 or more	0 1 2 3
5. Καπνίζετε πιο πολύ το πρωί που ξυπνάτε ή το απόγευμα;	Yes No	1 0
6. Καπνίζετε όταν είστε αδιάθετος /άρρωστος;	Yes No	1 0

Προσδιορισμός βαθμού εξάρτησης

Αντικειμενικές μέθοδοι

- Η μέτρηση της συγκέντρωσης της νικοτίνης ή του μεταβολίτη της κοτινίνη στο:
 - Αίμα
 - Ούρα
 - Πτύελα
- Μέτρηση του εκπνεόμενου CO:
 - Αφορά την λήψη νικοτίνης τις προηγούμενες ώρες
 - Δεν έχει την ακρίβεια της μέτρησης της νικοτίνης
 - Είναι εύκολη και φθηνή
 - **Ενισχύει άμεσα τον καπνιστή**

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Assessment	The 5 A's framework is a useful strategy for engaging patients in smoking cessation discussions. The 5 A's include: 1) Asking every patient about tobacco use, 2) Advising all tobacco users to quit, 3) Assessing the willingness of all tobacco users to make an attempt to quit, 4) Assisting tobacco users with their attempt to quit, and 5) Arranging follow-up.			
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Συμβουλευτική (Counseling)

- 1. Συμβουλή για διακοπή καπνίσματος επαγγελματία τρενέρια

**Evidence
Level I
Strength A**

Telephone counseling and quitters

- 2. Provides advice, encouragement and support (by specialist counselors to smokers who want to quit or
- 3. Γνω who have recently quit

**their own
only
effects**

**(RR 1.98) or
dual (RR 1.39)
Evidence A**

**Both increase quit
rates over that of
minimal support**

Counseling

Intensity

- Both minimal (<20 min in 1 visit) and intensive (≥ 20 min plus >1 follow-up visit) physician-advice interventions effectively increase the proportion of adults who successfully quit smoking and remain abstinent for ≥ 6 mo.
- There is a dose-response relationship between the intensity of counseling and cessation rates (i.e., more or longer sessions improve cessation rates).

Duration

- Brief, in-person behavioral counseling sessions (<10 min) effectively increase the proportion of adults who successfully quit smoking and remain abstinent for 1 y.
- Although less effective than longer interventions, even minimal interventions (<3 min) have been found to increase cessation rates in some studies.

Frequency

- Multiple sessions should be provided; according to the Public Health Service guidelines, patients should receive ≥ 4 in-person counseling sessions.
- Cessation rates may plateau after 90 min of total counseling contact time.

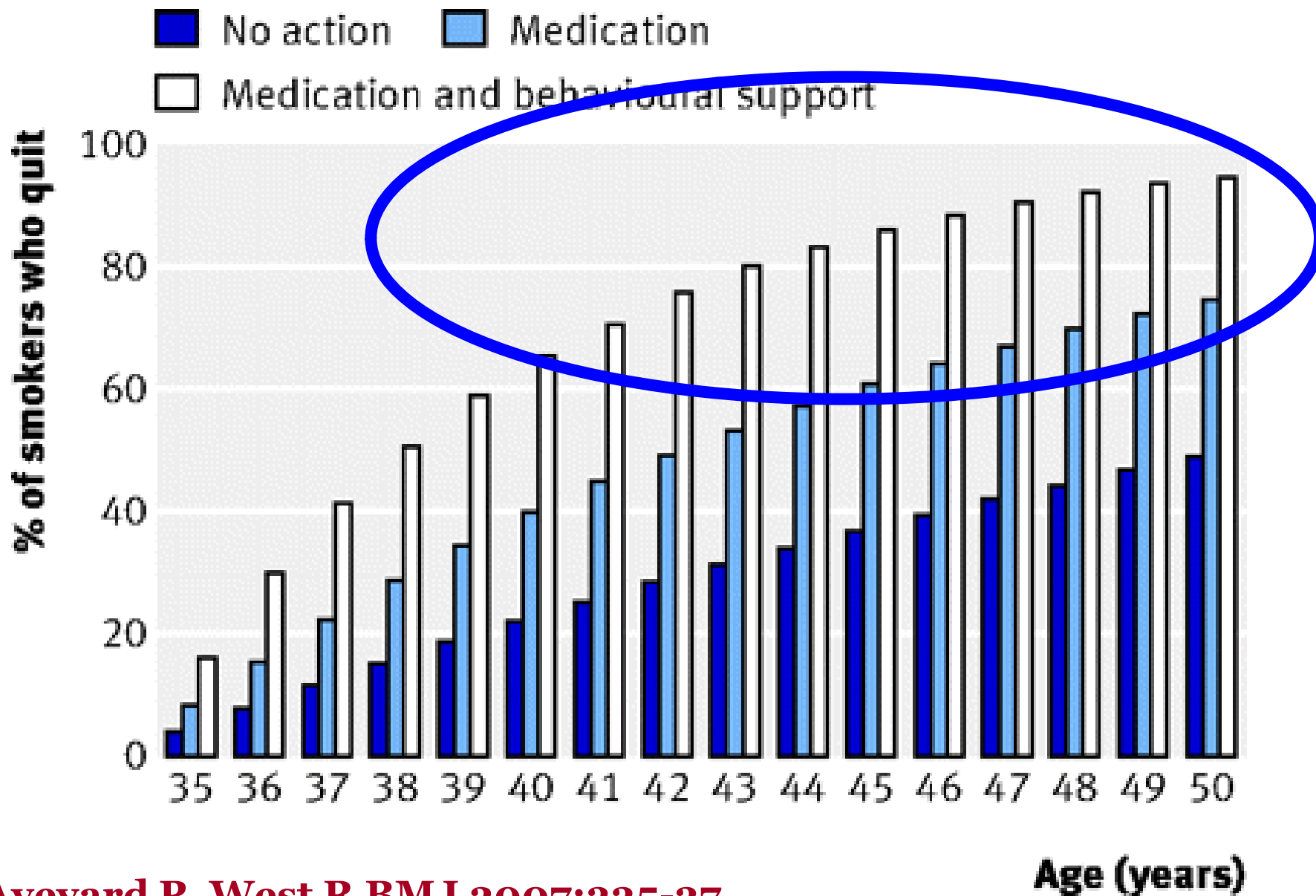
Αποτελεσματικές μέθοδοι διακοπής καπνίσματος

- Δύο τύποι προσέγγισης είναι αποδεδειγμένα αποτελεσματικοί:
 - Συμβουλευτική
 - Φαρμακοθεραπεία
- Τα καλύτερα αποτελέσματα επιτυγχάνονται με συνδυασμό των δύο προσεγγίσεων

Fiore MC. Treating tobacco use and dependence. Resp Care 2000;45:1200

West R. Smoking cessation guidelines for health professionals: an update. Thorax 2000;55:987

Simon JA. Smoking cessation counseling (intensive vs minimal). Am J Med 2003;114(7):555



Aveyard P. West R BMJ 2007;335-37

Εγκεκριμένη Φαρμακοθεραπεία

στη διακοπή του καπνίσματος

- Φάρμακα που μιμούνται τη δράση της νικοτίνης
 - *Υποκατάστατα νικοτίνης*
- Φάρμακα που δρουν στο ΚΝΣ
 - *Καθυστερώντας την αποδόμηση των νευρομεταβιβαστών*
 - *HCL Bupropion*
 - *Ενεργώντας απευθείας στους υποδοχείς $\alpha 4 \beta 2$*
 - *Varenicline*

JAMA 2009

Albert L Siu Ann Internal Med 2015;163:622

Φαρμακοθεραπεία για την Διακοπή του Καπνίσματος

- **Nicotine replacement therapy**
 - Recommended first line therapy
 - Long acting
 - Patch
 - Short acting
 - Gum
 - Inhaler
 - Nasal spray
 - Sublingual tablets/lozenges
- **Bupropion**
- **Varenicline**
 - Recommended first-line therapy (WHO, US, Europe, UK)
- **Nortriptyline**
 - Recommended second-line therapy (WHO, US)
- **Clonidine**
 - Recommended second-line therapy in some countries

↑ ↑ side effects:
dizziness
sedation, ↓ BP

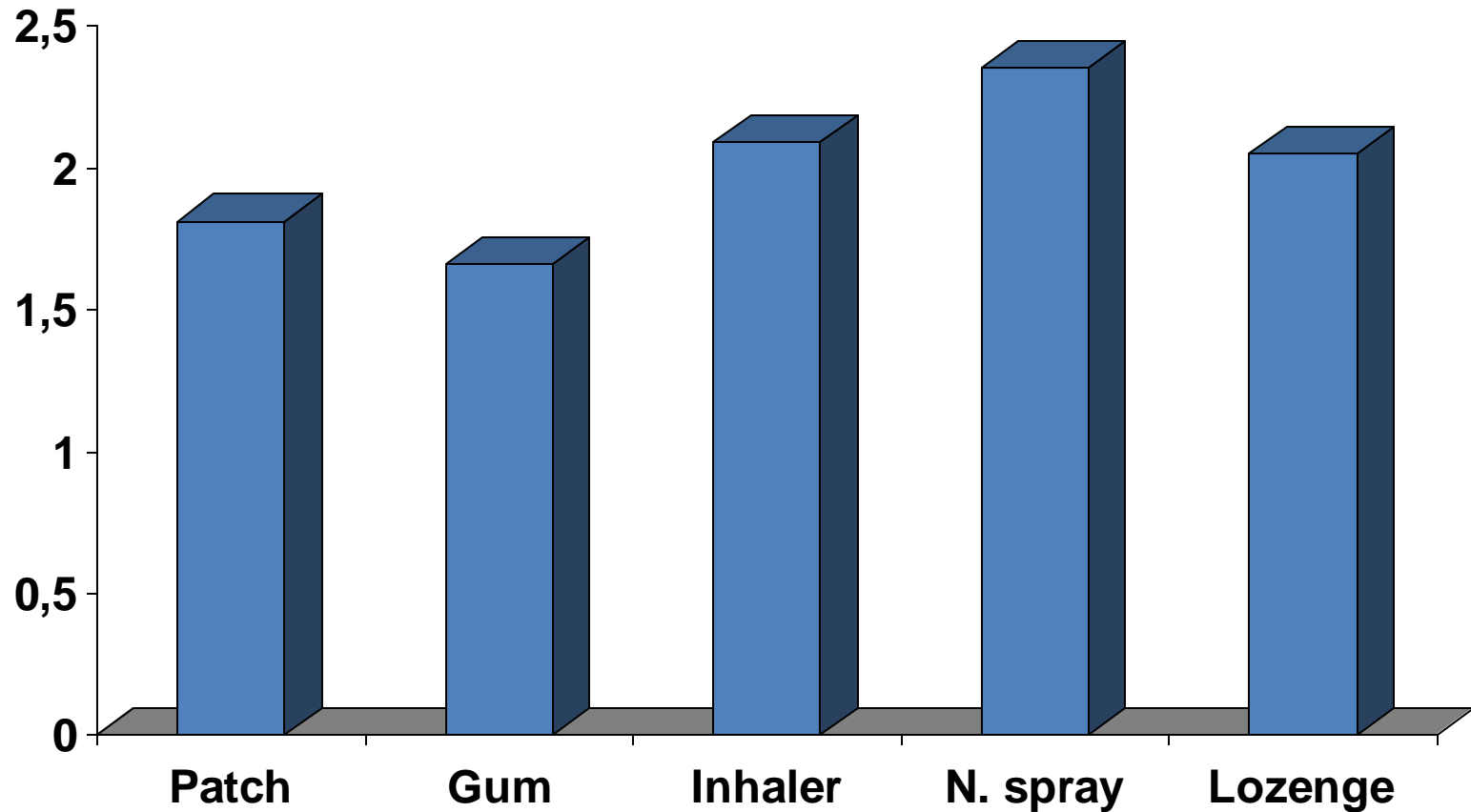
Θεραπεία υποκατάστασης της νικοτίνης

- NRT : διατίθεται σε διάφορες μορφές
 - Πλεονεκτήματα
 - Αποτελεσματικότητα
 - Ευκολία στη χρήση
 - Εύκολα διαθέσιμη (Readily available)
 - Όχι ακριβή
- Οι βραχείας δράσης μορφές :
 - Satisfy the positive effects of nicotine intake through smoking ⇒ reduce acute craving
- Η μακράς δράσης μορφή παρέχει χαμηλά αλλά σταθερά επίπεδα νικοτίνης
 - Can relieve nicotine withdrawal symptoms

Διαθέσιμες μορφές NRT

Type	Dosage	Dose /day	Comments	Disadvantages
Patch	Seven strengths: 5, 7, 10, 14, 15, 21 and 25 mg (16 or 24 hour release)	One	Change patch site daily, remove at bedtime if sleep disorders Overnight use may reduce early morning cravings Recommended for 6 to 2 weeks	Skin irritation. Slow delivery Wearing at night may cause sleep problems
Gum	2 mg, 4 mg	20	Flexible dosing Faster delivery of nicotine than patch Recommended for 6 to 2 weeks	No food or drink 15 min before use Jaw pain, mouth soreness, dyspepsia, hiccups
Inhaler	4 mg per cartridge 1 cartridge to be used every 1 to 2 hours while awake	6 to 16 cartridge	Flexible dosing mimics hand-to-mouth behavior Can be used up to 6 months	Mouth and throat irritation Frequent dosing necessary
Nasal spray	0.5 mg per spray 1 to 2 doses every hour	< 40	Flexible dosing Fastest delivery of nicotine among all products Reduces cravings within a few minutes Can be used for 3 to 6 months	Frequent dosing Nose and eye irritation Cough
Sublingual tablets/ Lozenge	2 mg, 4 mg 1 lozenge to be used every 1 to 2 hours while awake		Flexible dosing Faster delivery of nicotine (like gum) More socially acceptable than the gum Recommended for up to 12 weeks	No food or drink 15 min before use Dyspepsia, mouth soreness, hiccups, nausea, flatulence.

Odds ratio of smoking cessation with different NRTs



Fiore MC. Treating tobacco use and dependence: 2008

Silagy C et al. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2015(3):CD000146

Αντικαταθλιπτικά

- **Bupropion SA:** dopaminergic and noradrenergic profile

Grade A

- *Mechanism of action for smoking cessation*
- *Possibly works via multiple mechanisms*
- *Efficacy comparable to nortriptyline*

**Dose: 150mg/day (3-6 days)
150mg twice daily thereafter
SOS : never >300mg/day**

- **Nortriptyline**

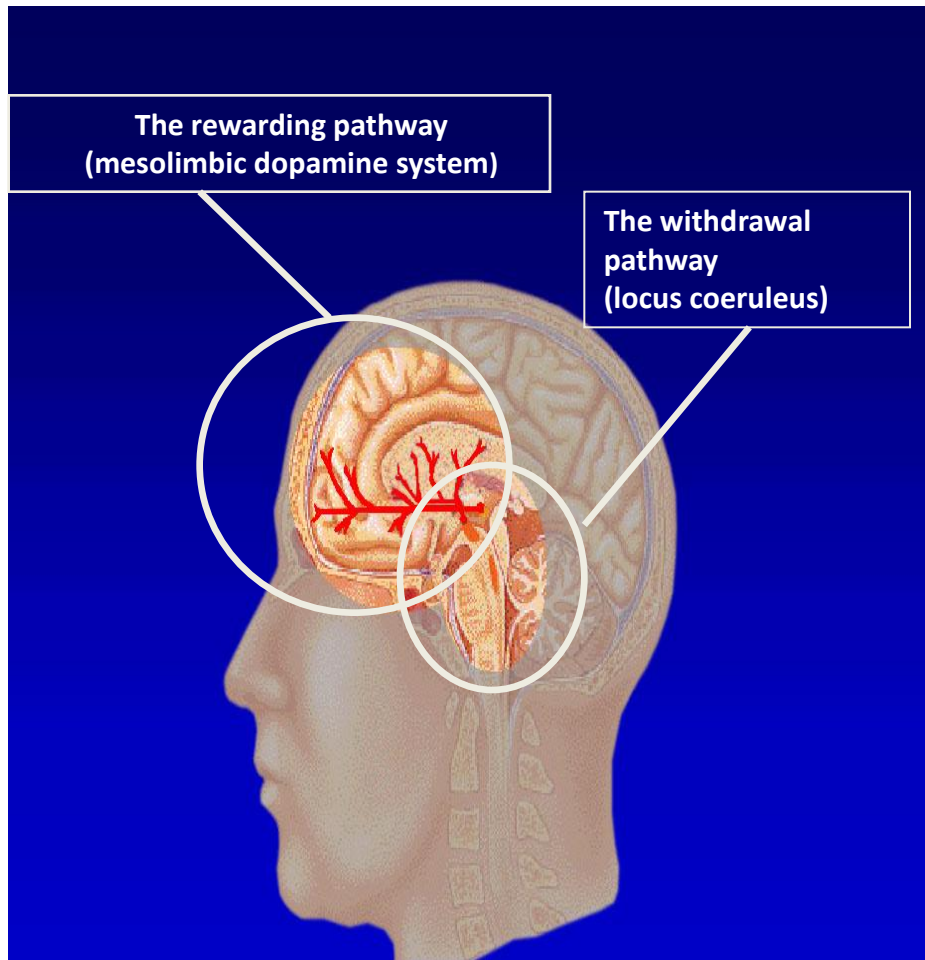
- *A tricyclic antidepressant with mostly noradrenergic properties*
- *Effective but the limited number of trials and the side effects make it second-line intervention*

Grade B

75mg/day

Mechanism of action

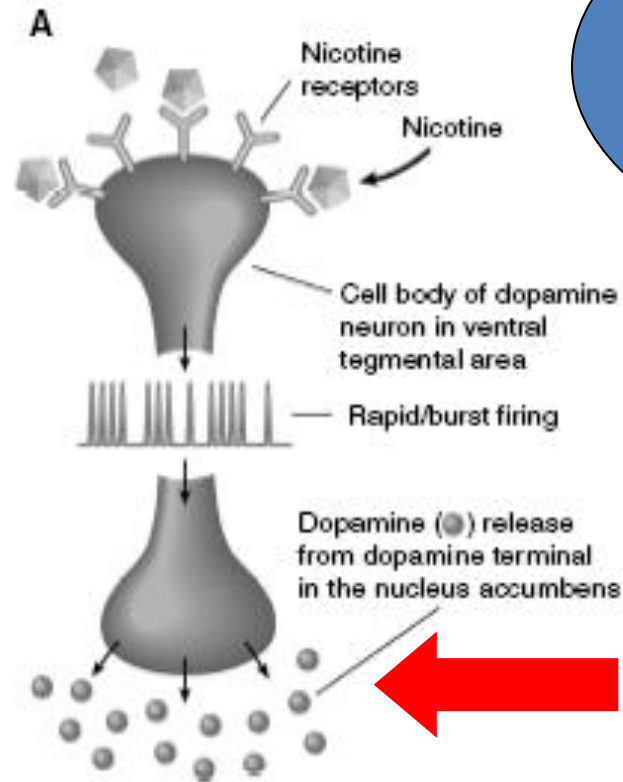
- Bupropion is a beta phenylethylamine derivative
 - Explains its stimulant property
- It preferentially blocks norepinephrine and dopamine reuptake in the mesolimbic system and the nucleus accumbens
- It is also an antagonist of nicotinic receptors
 - Hence, it blocks the reinforcing effects of nicotine



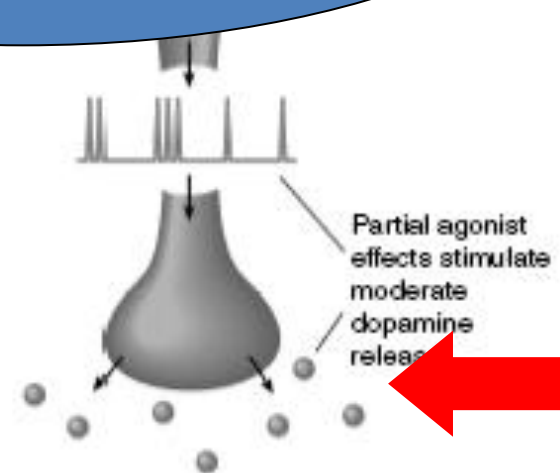
Partial Agonist /antagonist of α4β2 nicotinic receptors

- **Varenicline**
- Cytisine

Varenicline: Mechanism of action

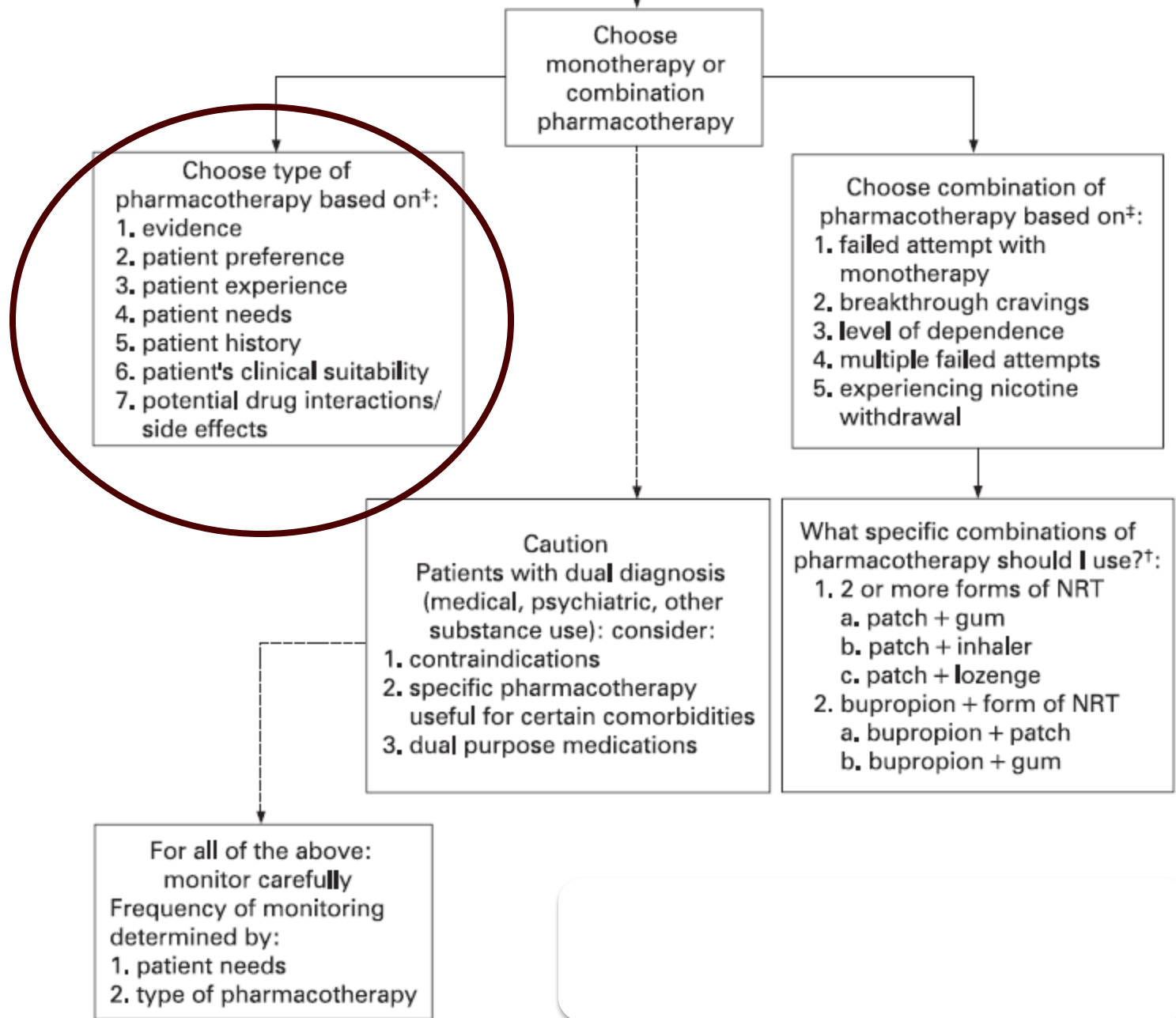


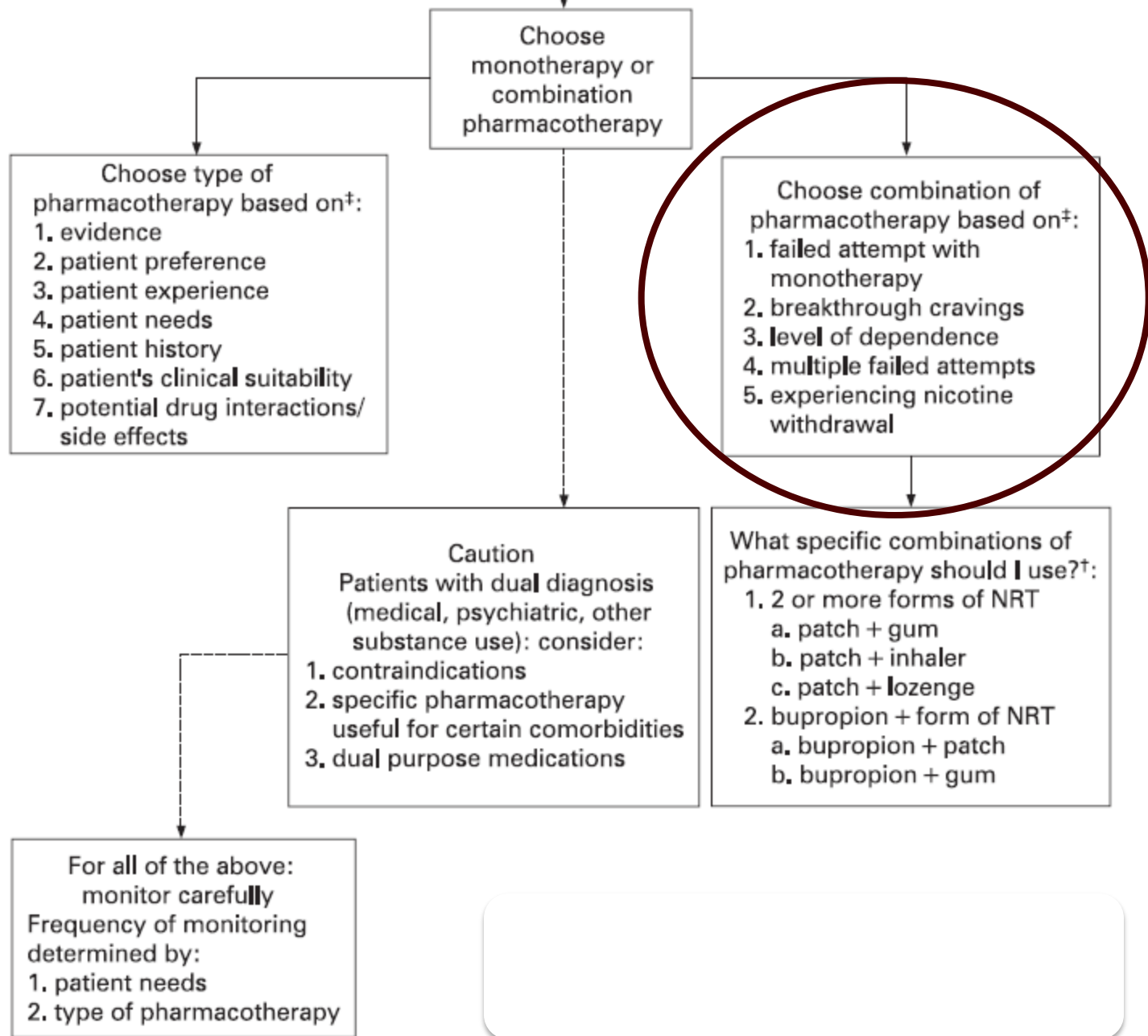
Dose: 0.5 mg for 3 days
0.5 mg bid for 4 days
And
1mg bid to the end of the treatment

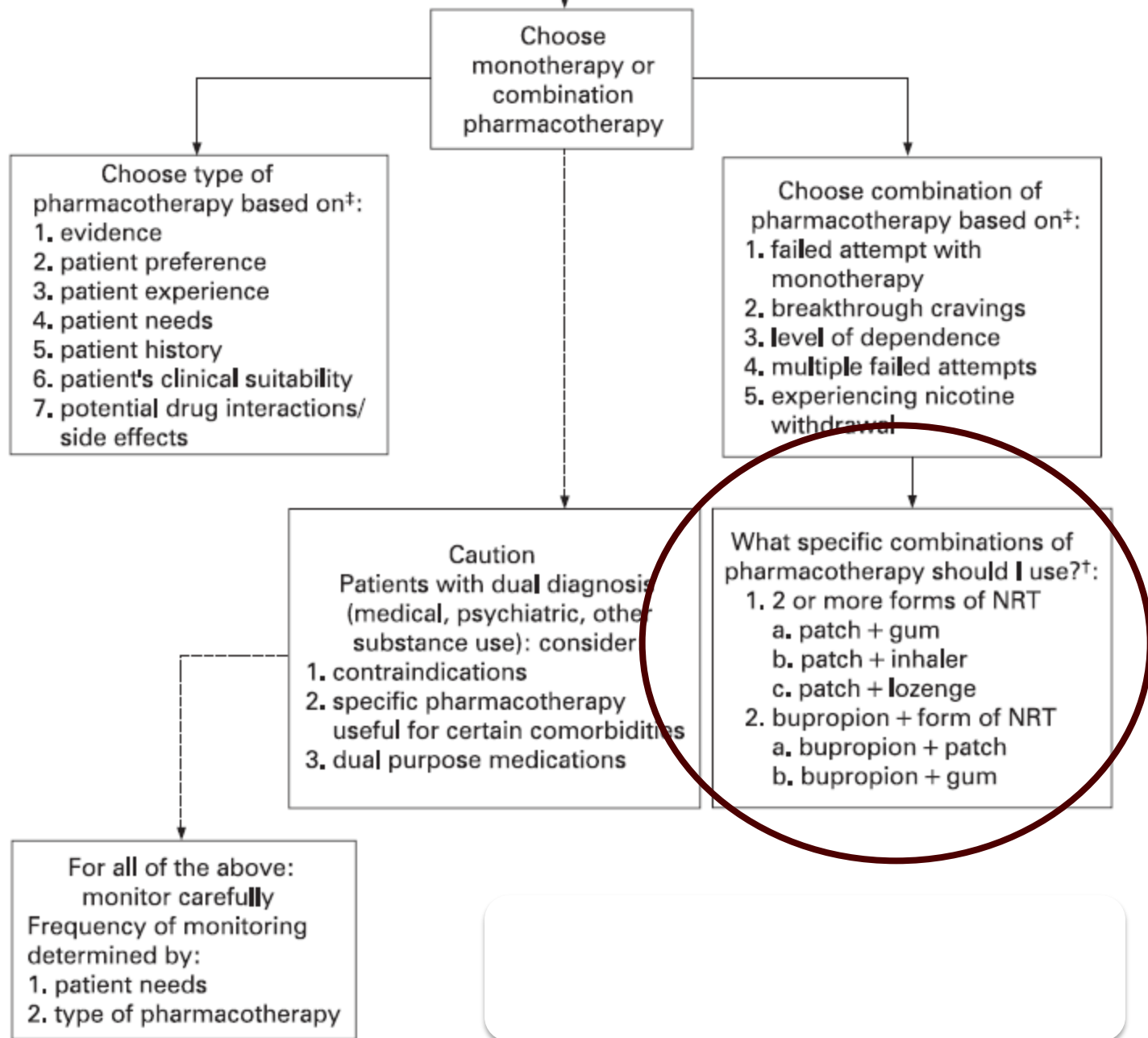


Fould J Int J Clin Pract 2006

Gillian M. CNS Drugs 2006;20 (1): 945-60

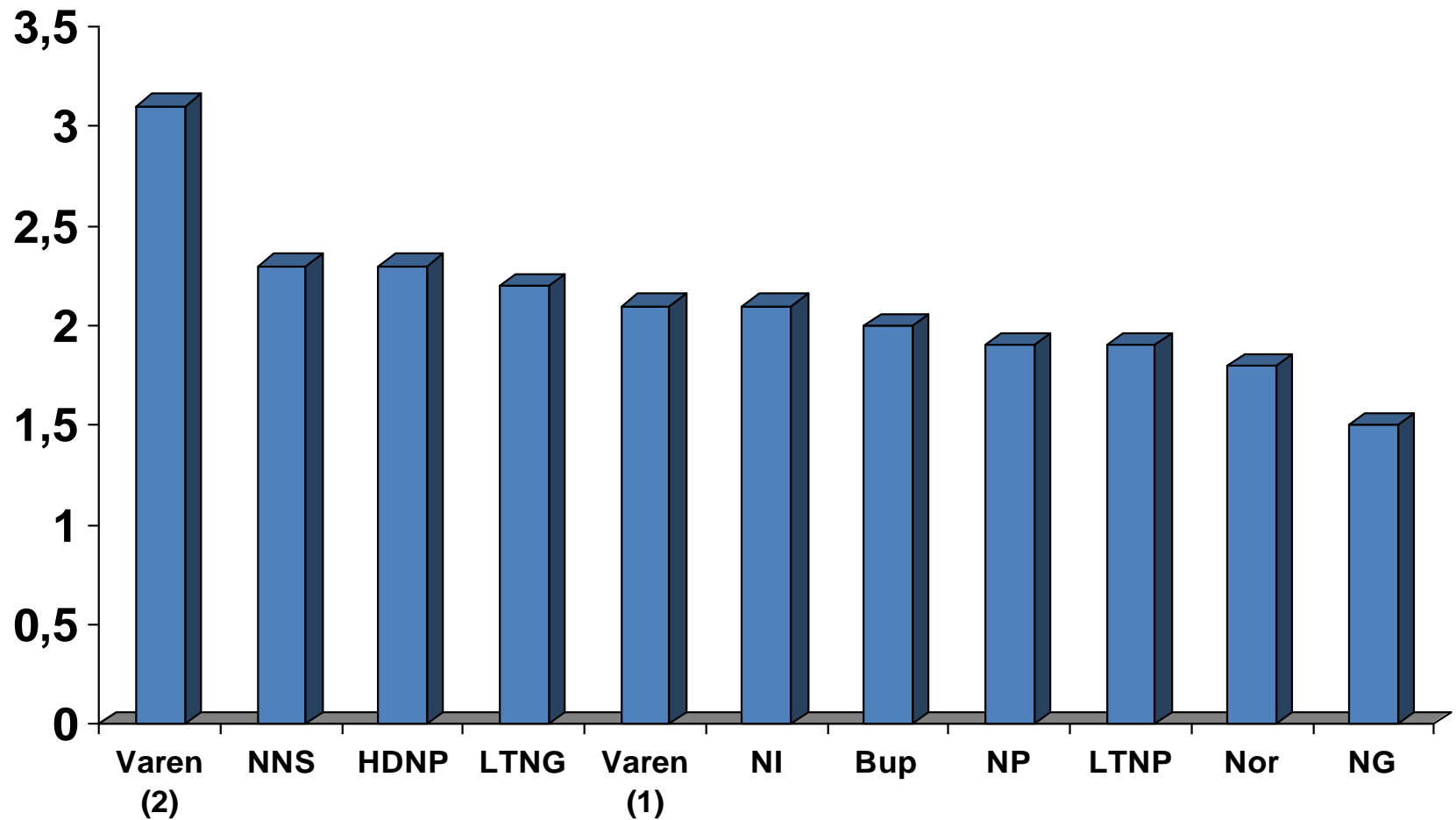




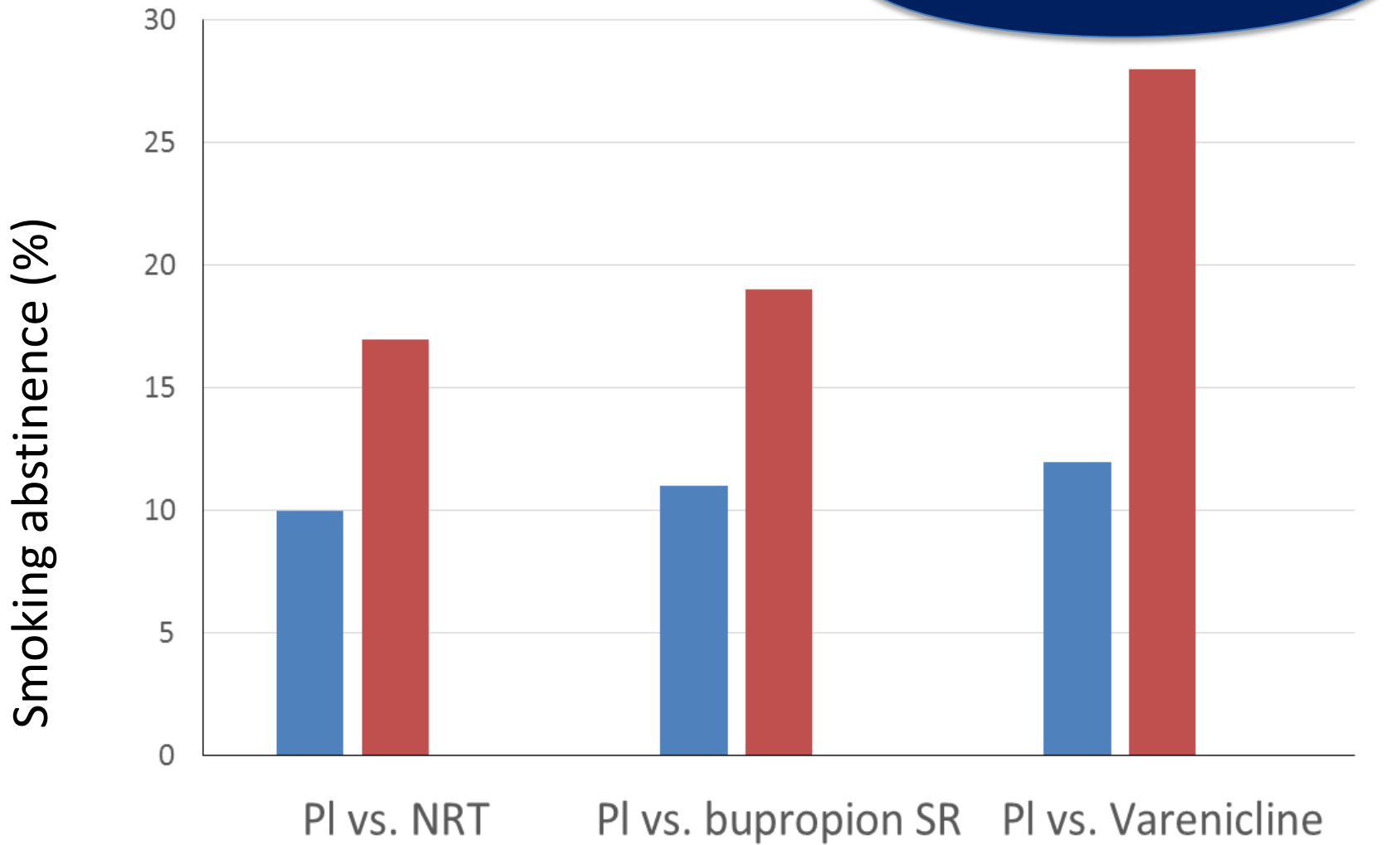


Odds Ratio

6months abstinence



Taylor J Mayo Clin Proc 2009;84(8): 730-36



Albert L Siu Ann Internal Med 2015;163:622

Combination pharmacotherapy

- Varenicline + NRT

- Ramon Varenicline + 21 mg Patch Nicotine

- NO Differences / in sub groups better results
 - 24 weeks: (smok >29 cig/day)
 - OR 1.46% quit rate vs 32.6%

- Koegelenberg J(smok >20 cigarettes/day)

- Varenicline + 15 mg Patch Nicotine

- 24 weeks: 49% quit rate vs 32.6%

- Varenicline + Bupropion

- Ebbert JO J

- 12,26, and 52 weeks NO significant differences
 - in sub group (heavy smokers) better results

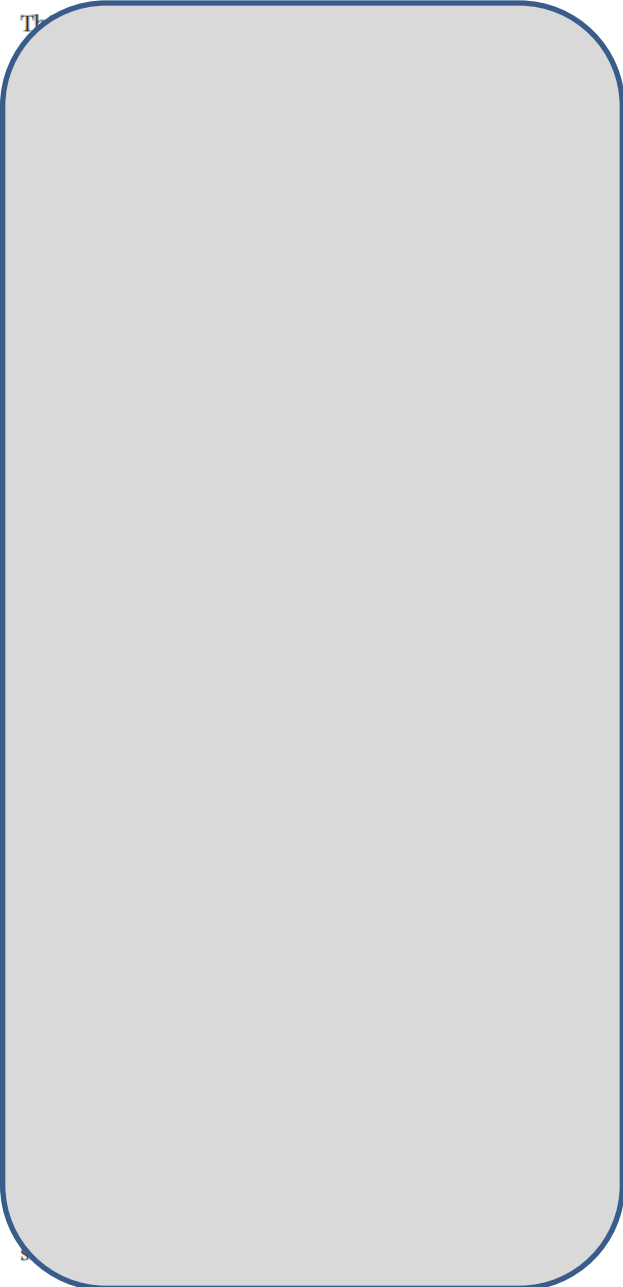
Intervention	Effectiveness	Affordability
Brief opportunistic advice from a health-care worker		Globally affordable
Printed self-help materials		Globally affordable
Proactive telephone support		Globally affordable
Automated text messaging		Globally affordable
Face-to-face behavioural support		Affordable in middle- and high-income countries
Nicotine replacement therapy		Affordable in middle- and high-income countries
Cytisine		Globally affordable
Bupropion		Affordable in middle- and high-income countries
Nortriptyline		Globally affordable
Varenicline		Affordable in middle- and high-income countries

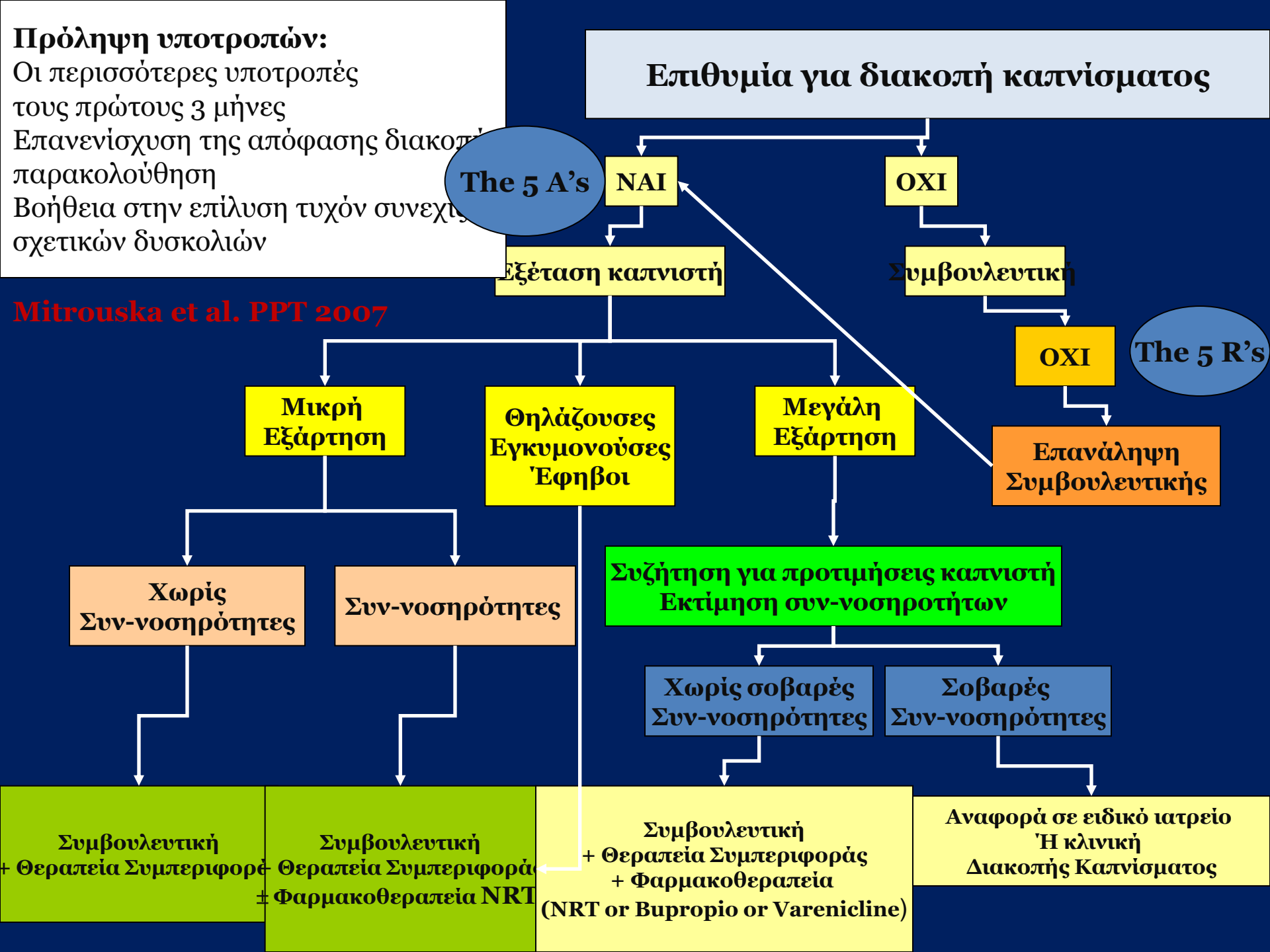
Table 1: First-line pharmacologic treatment of tobacco dependence				
Drug	Dose	Duration of treatment	Contraindications	Adverse effects*
Nicotine replacement therapy	Dose is adjusted to level of nicotine dependence and is decreased progressively over treatment period Patch: 21-42 mg/d initially Gum: 8-10 pieces (2 or 4 mg each) per day Inhaler: 4-6 puffs per day Lozenge: 9-20 lozenges per day	8-12 weeks; can be longer (up to 1 year) for the prevention of relapse	Patch: allergy to constituent of nicotine patch	Patch: skin irritation, sleep disturbance Gum or lozenge: mouth irritation, sore jaw, dyspepsia, hiccups Inhaler: mouth and throat irritation, cough
Bupropion, sustained release (Zyban)	150 mg/d for first 3 days, then 300 mg/d	8 weeks; can be longer (up to 1 year) for the prevention of relapse	Seizure, central nervous system tumour, bipolar disorder, alcohol withdrawal, benzodiazepine withdrawal, use of monoamine oxidase inhibitor, anorexia, bulimia, liver disease	Insomnia, seizure, gastrointestinal disturbance, jitteriness
Varenicline (Champix)	0.5 mg/d for first 3 days, then 0.5 mg twice daily for the next 4 days and 1 mg twice daily thereafter	12 weeks; can be longer (up to 24 weeks) for the prevention of relapse	None	Nausea, vomiting, constipation, flatulence, bad taste in the mouth, abnormal dreams, sleep disturbance

*Most frequent adverse events.

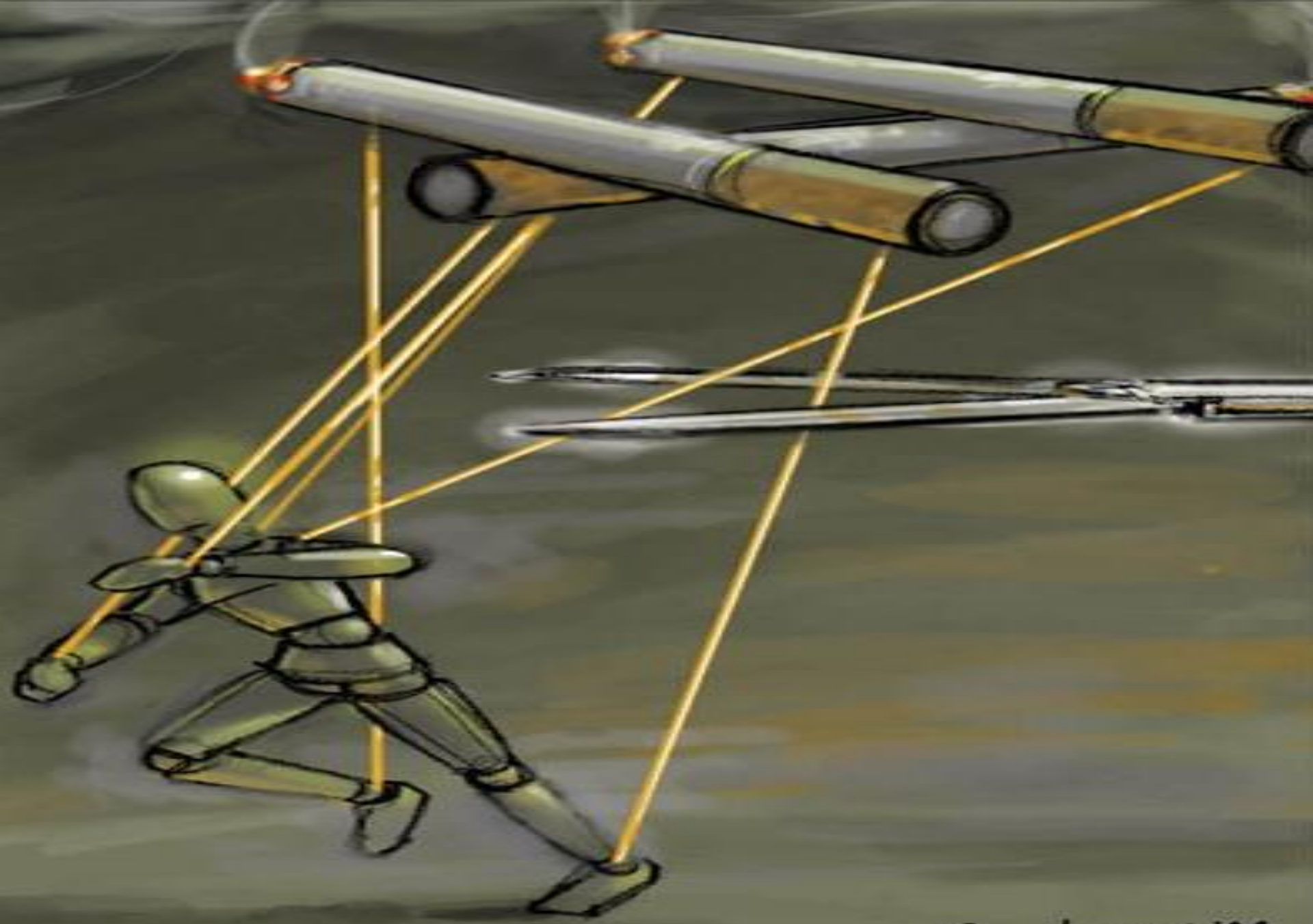
Taylor J Mayo Clin Proc 2012;84(8): 730-36

Διάρκεια Θεραπείας

- Υποκατάστατα νικοτίνης
 - 2 – 4 μήνες
- Υδροχλωρική βουπροπιόνη (Zyban)
 - 8 εβδομάδες
 - 150mg x 2
- Βαρενικλίνη (Champix)
 - 3 μήνες
 - 1mg x 2



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C. Lynn



	Nicotine Gum	Nicotine Lozenge	Nicotine Nasal Spray	Nicotine Inhaler	Nicotine Patch	Bupropion SR 150	Varenicline
Time to peak venous nicotine level	15-30 min	25-30 min	5-15 min	15 min	6-12 h	Not applicable	Not applicable
Dosing	1 piece every 1-2 h as needed, then taper. Do not eat or drink 15 min before or during use	1 piece every 1-2 h as needed, then taper. Do not eat or drink 15 min before or during use	1 inhalation each nostril every 1-2 h as needed, then taper	Multiple inhalations over 20 min every 1-2 h as needed, then taper	1 patch daily for 16 or 24 h, then taper	150 mg daily for 3 d, then 150 mg twice daily. Begin therapy 1-2 wk prior to quit date	0.5 mg daily for 3 d, twice daily for 4 d, then 1 mg twice daily. Begin therapy 1 wk prior to quit date
Dose adjustment	If ≤ 24 cig/d: 2 mg; if ≥ 25 cig/d: 4 mg	First cig > 30 min after waking: 2 mg; first cig ≤ 30 min after waking: 4 mg	Not applicable	Not applicable	If ≥ 10 cig/d: start 21 mg; if ≤ 10 cig/day: start 14 mg	Not applicable	Not applicable
Daily maximum	24 pieces gum	20 lozenges	40 doses (80 sprays)	16 cartridges (80 inhalations/cartridge)	1 patch	2 tablets	2 tablets
Duration of therapy	3 mo	3-6 mo	3-6 mo	6 mo	3 mo	6 mo	3-6 mo
Common side effects	Orogastric irritation, diarrhea	Orogastric irritation, hiccups	Nasal irritation, bronchospasm, asthmatics	Oropharyngeal irritation, bronchospasm, asthmatics	Insomnia, skin irritation	Insomnia, lowered seizure threshold, increased suicidality	Insomnia, vivid dreams, nausea
USFDA pregnancy category	C	C	D	D	D	C	C
Odds ratio vs placebo, 6-mo smoking abstinence	1.5 (1.2-1.7)	2.0 (1.4-2.8)	2.3 (1.7-3.0)	2.1 (1.5-2.9)	1.9 (1.7-2.2)	2.0 (1.8-2.2)	3.1 (2.5-3.8)

Κριτήρια μεγάλης εξάρτησης στην νικοτίνη

- FTND score ≥ 6 points (out of 10) και
- Επίπεδα κοτινίνης στον ορό $\geq 250\text{mg/ml}$ ορού
- Πρώτο τσιγάρο < 30 λεπτά μετά την αφύπνιση
 - Αυτό το κριτήριο δεν είναι υποχρεωτικό αλλά όταν υπάρχει προσφέρει ένα αξιόπιστο κλινικό προγνωστικό δείκτη υψηλής εξάρτησης

Fagestrom. Addict Behav. 1978;3:235-41

Heatherton. Br J Addict 1991; 86:1119-27

Sachs Eur Respir J. 1996;9:629-31

West R Addiction 2015

Intervention versus comparison	Delivered by	Delivered to	Percentage point increase in 6–12-month abstinence (95% CI)	Projected percentage point increase in 6–12-month abstinence compared with no intervention
Brief advice from a physician versus no intervention	Physicians	Smokers attending a surgery	2 (2–3)	2
Printed self-help materials versus nothing	Health-care provider (e.g. health promotion organization)	Smokers wanting help with stopping and willing to set a quit date	2 (1–3) ^a	2
Proactive telephone support versus reactive telephone support	Trained stop-smoking practitioners	Smokers wanting help with stopping and willing to set a quit date	3 (2–4) ^a	5
Automated text messaging versus non-smoking-related messaging	Systems providers	Smokers wanting help with stopping and willing to set a quit date	4 (3–5) ^a	4
Face-to-face individual behavioural support versus brief advice or written materials	Trained stop-smoking practitioners	Smokers wanting help with stopping and willing to set a quit date	4 (3–5) ^b	6
Face-to-face group-based behavioural support versus brief advice or written materials	Trained stop-smoking practitioners	Smokers wanting help with stopping and willing to set a quit date	5 (4–7) ^b	7
Single NRT versus placebo	Health professionals ^c	Smokers wanting help with stopping and willing to set a quit date	6 (6–7) ^d	6
Dual form/combination NRT versus placebo	Health professionals ^c	Smokers wanting help with stopping and willing to set a quit date	11 ^e	11
Cytisine versus placebo	Health professionals	Smokers wanting help with stopping and willing to set a quit date	6 (4–9) ^f	6
Bupropion versus placebo	Health professionals	Smokers wanting help with stopping and willing to set a quit date	7 (6–9) ^f	7
Nortriptyline versus placebo	Health professionals	Smokers wanting help with stopping and willing to set a quit date	10 (6–15) ^f	10
Varenicline versus placebo	Health professionals	Smokers wanting help with stopping and willing to set a quit date	15 (13–17) ^f	15

COUNSELING

Format

- In-person behavioral counseling sessions (individual or group counseling)
- Telephone counseling
- Tailored, print-based self-help materials

Provider

- In-person behavioral counseling sessions: various types of primary care providers, including physicians, nurses, psychologists, social workers, and cessation counselors
- Telephone counseling: professional counselors or health care providers who are trained to offer advice over the telephone

Content

- Assessment of smoking status
 - Ask every patient about tobacco use
 - Advise all tobacco users to quit
 - Assess willingness of all tobacco users to make an attempt to quit
 - Assist all tobacco users with their attempt to quit
 - Arrange follow-up
- Effective counseling interventions provide social support and training in practical problem-solving skills

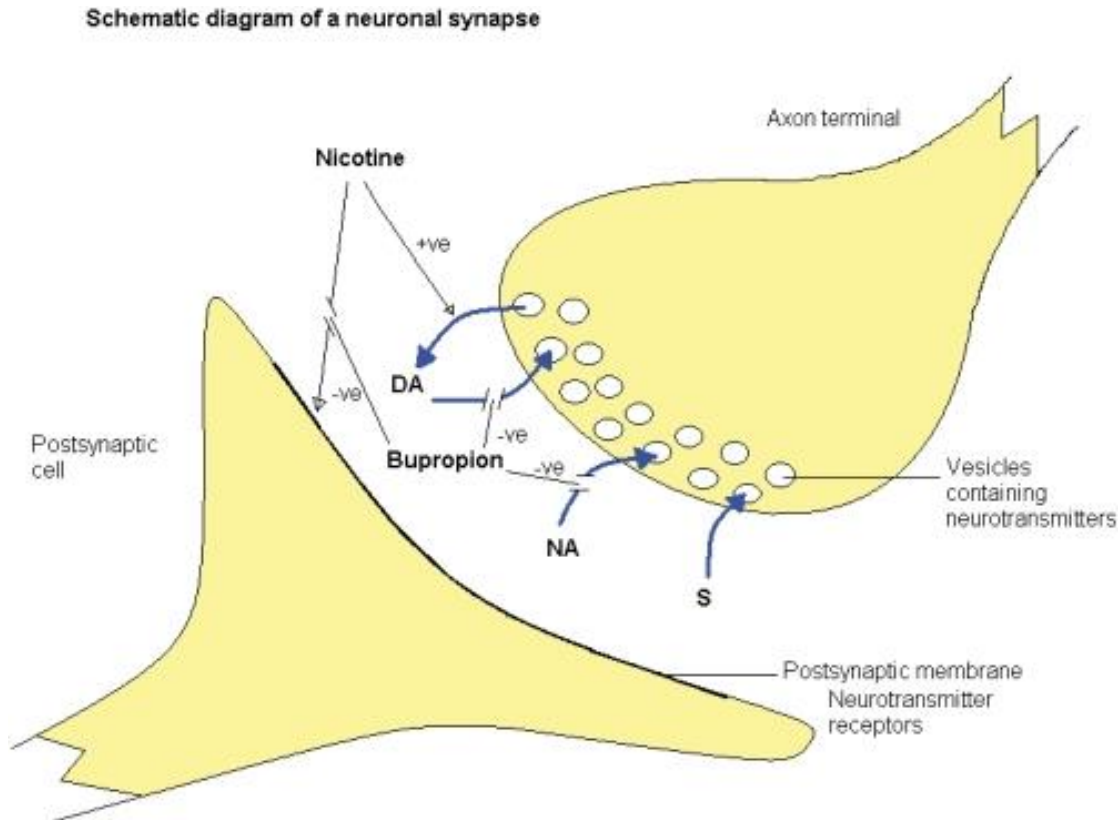
Training in problem-solving skills includes helping persons who smoke to recognize situations that increase their risk for smoking, develop coping skills to overcome common barriers to quitting, and develop a plan to quit

Basic information about smoking and successful quitting should also be provided

Complementary practices that improve cessation rates include motivational interviewing, assessing readiness to change, and offering more intensive counseling or referrals

Albert L Siu Ann Internal
Med 2015;163:622

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Wilkes S IJ COPD 2008;3 45-53