

# Smoking cessation

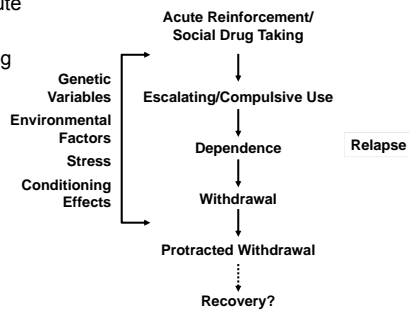
By

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 Department of Family medicine,  
 Faculty of Medicine Ramathibodi Hospital,  
 Mahidol University

# Neurobiology of Addiction

## Stages of Addiction

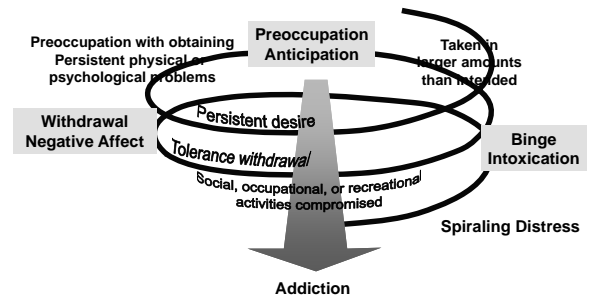
- Begins with social drug taking and acute reinforcement
- Pattern of escalating compulsive use
- Dependence



Le Moal et al. *Eur Neuropsychopharmacol.* 2007;17:377-393.

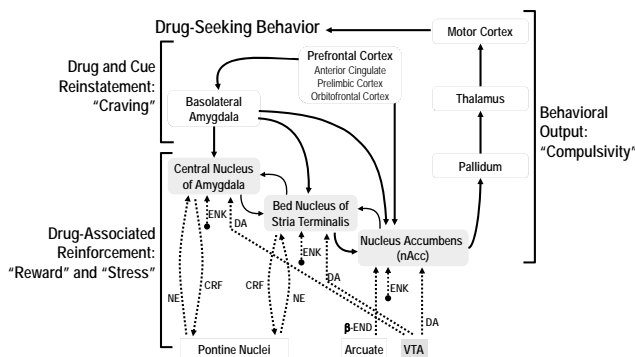
## Spiraling Cycle of Addiction (DSM-IV)

- The 3 major components of the addiction cycle are preoccupation-anticipation, binge-intoxication, and withdrawal-negative affect
- The cycle is conceptualized as a spiral that increases in amplitude with repeated experience, ultimately resulting in the pathologic addictive state



Koob. *Eur Neuropsychopharmacol.* 2003;13:442-452.

## Neurocircuits That Underlie Addiction



NE=norepinephrine, ENK=enkephalin, CRF=corticotropin-releasing factor, DA=dopamine, β-END=β-endorphin.  
 Le Moal et al. *Eur Neuropsychopharmacol.* 2007;17:377-393.

## Neurobiologic Basis for Relapse

- Relapse occurs in response to stimulation by compulsive drive circuits and deficits in inhibitory restraint

### Compulsive Drive Circuits

- Priming
- Drug cues
- Obsessive thoughts (craving)
- Stress

### Inhibitory Control Deficits

- Impulsivity (automaticity)
- Decision making

Adinoff. *Harv Rev Psychiatry.* 2004;12:305-320.

## Summary: Neurobiology of Addiction

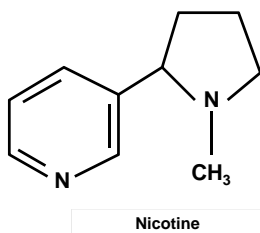
- Addiction is a multistep process
- Multiple neurocircuits are involved in the craving, reward, stress, and compulsivity associated with addiction
- Relapse occurs in response to stimulation by compulsive drive circuits and deficits in inhibitory restraint

## Nicotine Dependence

- Action of nicotine in the central nervous system
- Neurobiologic and physiologic effects of tobacco dependence

## Nicotine Dependence: DSM-IV-TR Criteria

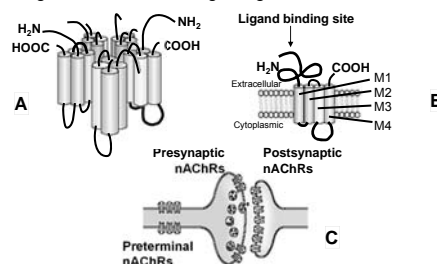
- 3 or more of the following symptoms within a 1-year time span:
  - Tolerance to nicotine with decreased effect and increasing dose to obtain same effect
  - Withdrawal symptoms with cessation
  - Persistent desire to smoke despite efforts to decrease intake
  - Extensive time spent smoking or purchasing tobacco
  - Postponing work, social, or recreational events in order to smoke
  - Continuing to smoke despite health hazards



American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision*. Washington, DC: American Psychiatric Association; 2000; <http://www.intox.org/databank/documents/supplem/suppl/sup2.htm>. Accessed October 19, 2007.

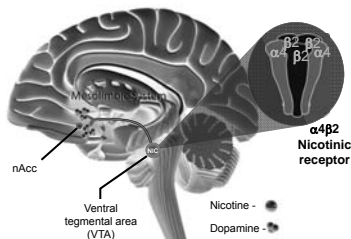
## Neuronal Nicotine Acetylcholine Receptor

- Nicotine binds preferentially to nicotinic acetylcholinergic receptors (nAChRs) in the central nervous system
- When nicotine binds to the nAChR, the receptor complex undergoes a conformational change, allowing the channel gate to open, permitting the passage of cations, resulting in signal transmission



Laviolette et al. *Nat Rev Neurosci*. 2004;5:55-65.

## Mechanism of Action of Nicotine in the Central Nervous System

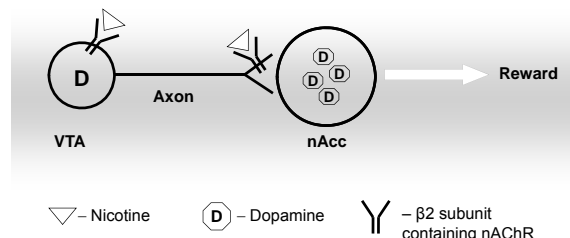


- The  $\alpha 4 \beta 2$  nicotinic receptor in the VTA mediates the effects of nicotine in the central nervous system
- After nicotine binds to the  $\alpha 4 \beta 2$  nicotinic receptor in the VTA, it results in a release of dopamine in the nAcc, which is believed to be linked to reward

nAcc= Nucleus Accumbens. Adapted from Picciotto et al. *Nicotine Tob Res*. 1999;1:S121-S125.

## Nicotine Stimulates Dopamine Release

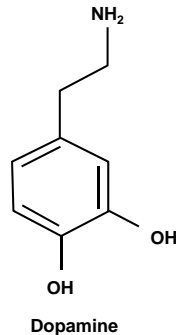
- Nicotine activates  $\alpha 4 \beta 2$  nicotinic receptors in the VTA, resulting in dopamine release at the nAcc. This may result in the short-term reward/satisfaction associated with cigarette smoking



nAcc= Nucleus Accumbens; VTA= Ventral Tegmental Area. Adapted from Picciotto et al. *Nicotine Tob Res*. 1999;1:S121-S125.

## Role of Dopamine in Nicotine Addiction

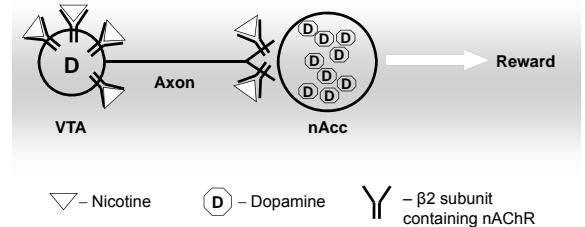
- Rewarding effects of nicotine are dependent on mesolimbic dopamine-mediated transmission
- In nicotine-dependent patients, the drive for continued drug use results from the need for heightened dopamine concentrations



Adinolf. *Harv Rev Psychiatry*. 2004;12:305-320. <http://www.biopsychiatry.com/dopamine/dopamine.jpg>. Accessed May 1, 2007.

## Chronic Nicotine Exposure: Up-Regulation of Nicotine Receptors

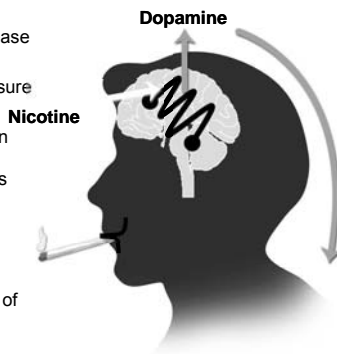
- With chronic exposure, nicotine stimulates  $\alpha 4\beta 2$  nicotinic receptor activation and desensitization, followed by  $\alpha 4\beta 2$  nicotinic receptor up-regulation and an increase in the number of  $\alpha 4\beta 2$  nicotinic receptors



Adapted from Picciotto et al. *Nicotine Tob Res*. 1999;1:S121-S125; Corringier et al. *J Phys Paris*. 2006;99:162-171.

## The Cycle of Nicotine Addiction

- Nicotine binding causes an increase in release of dopamine
- Dopamine gives feelings of pleasure and calm
- The dopamine decrease between cigarettes leads to withdrawal symptoms of irritability and stress
- The smoker craves nicotine to restore pleasure and calmness
- Smokers generally titrate their smoking to achieve maximal stimulation and avoid symptoms of withdrawal and craving



Jarvis. *BMJ*. 2004;328:277-279; Picciotto et al. *Nicotine Tob Res*. 1999;1:S121-S125.

## Role of Environmental Stimuli in Nicotine Dependence

- Environmental/social stimuli associated with smoking play a role in reinforcing nicotine dependence
- Nonnicotine stimuli are important in both motivating and maintaining smoking behavior
- Role of environmental vs pharmacologic stimuli in nicotine dependence varies between men and women

**Direct pharmacologic effects of nicotine are necessary but not sufficient to explain tobacco dependence; these effects must take into account the environmental/social context in which the behavior occurs**

Caggiula et al. *Physiol Behav*. 2002;77:683-687.

## Summary: Nicotine Dependence

- Nicotine dependence is a well-defined addictive disorder
- Nicotine's effects on the  $\alpha 4\beta 2$  receptors in the Ventral Tegmental Area (VTA) results in
  - Acute dopamine release and short-term reward
  - Chronic receptor activation, desensitization, and up-regulation
- The dopaminergically mediated physical and psychological rewards of smoking reinforce repeat behavior
- Environmental/social stimuli associated with smoking play a role in reinforcing nicotine dependence

## Nicotine Withdrawal

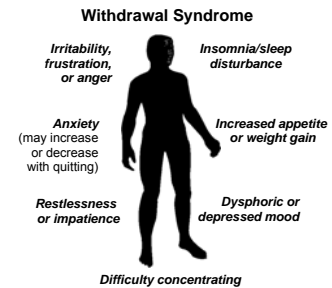
“Why do people smoke . . . to relax; for the taste; to fill the time; something to do with my hands. . . . But, for the most part, people continue to smoke because they find it too uncomfortable to quit”

Philip Morris, 1984

Philip Morris. Internal presentation. 1984, 20th March; Kenny et al. *Pharmacol Biochem Behav.* 2001;70: 531-549.

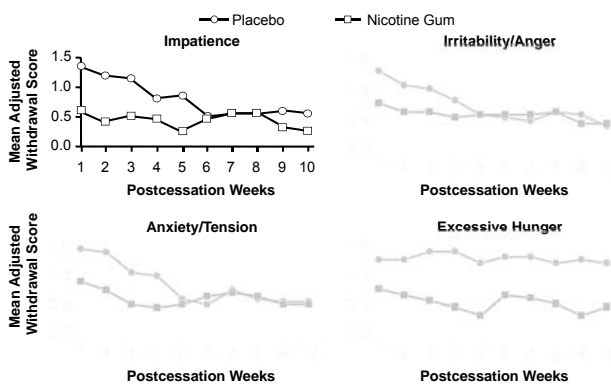
## Nicotine Withdrawal

- Nicotine withdrawal syndrome consists of both somatic and affective symptomatology



American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision.* Washington, DC: American Psychiatric Association; 2000.

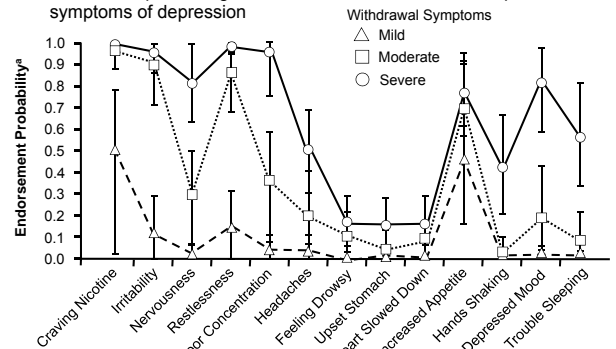
## Select Withdrawal Symptoms Over Time



N = 40. Mean adjusted withdrawal scores are from an analysis of covariance with baseline cigarettes per day and baseline scores on the items shown as covariates. Gross et al. *Psychopharmacology.* 1989;98:334-341.

## Nicotine Withdrawal: Severity

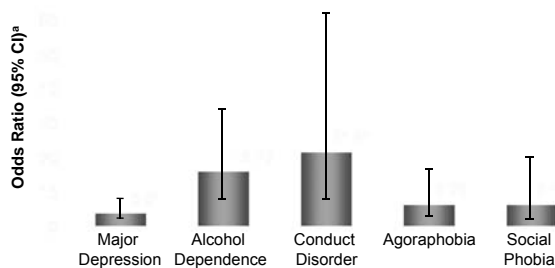
- Smokers experiencing severe withdrawal have the most pronounced symptoms of depression



\*Classes of withdrawal syndrome are defined by groups of respondents who endorsed similar combinations of symptoms. Estimates of prevalence for different classes of withdrawal were obtained along with expected frequencies of endorsement for each symptom of withdrawal by type. Madden et al. *Addiction.* 1997;92(7):889-902.

## Severity of Withdrawal and Psychiatric Disorders

- Smokers with a history of psychiatric disorders have a higher likelihood of experiencing severe withdrawal



\*The ratio of the odds of development of disease in exposed persons to the odds of development of disease in nonexposed persons. Madden. *Addiction.* 1997;92(7): 889-902.

## Summary: Nicotine Withdrawal

- Nicotine withdrawal syndrome consists of both somatic and affective symptomatology
- Smokers experiencing severe withdrawal have the most pronounced symptoms of depression
- Smokers with a history of psychiatric disorders have a higher likelihood of experiencing severe withdrawal

## Objective

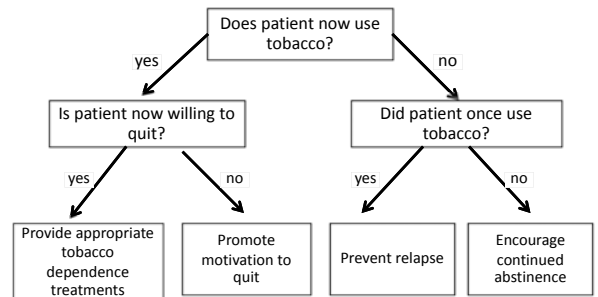
- To guide clinicians providing brief intervention. The “5A’s” model for treating tobacco use and dependence.
- To know medications for treating tobacco use and dependence.

211.09

Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence:2008 Update. Clinical Practice Guideline. Rockville,MD: U.S. Department of Health and Human Service. May 2008.

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## Algorithm for treating tobacco use



211.09

Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence:2008 Update. Clinical Practice Guideline. Rockville,MD: U.S. Department of Health and Human Service. May 2008.

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## Clinical Interventions for tobacco Use and Dependence

- Brief interventions
- Medications for treating tobacco use and dependence

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## Brief intervention

The goal of these strategies is clear :

- To change clinical culture and practice patterns
- To ensure that every patient who used tobacco is identified, advised to quit, and offered scientifically sound treatment

25.09.09

Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence:2008 Update. Clinical Practice Guideline. Rockville,MD: U.S. Department of Health and Human Service. May 2008.

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## Brief interventions with 3 types of patients

- Current tobacco users willing to make a quit attempt at this time.
- Current tobacco users unwilling to make a quit attempt at this time.
- Former tobacco users who have recently quit.

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Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence:2008 Update. Clinical Practice Guideline. Rockville,MD: U.S. Department of Health and Human Service. May 2008.

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## The five major components (the “5A’s”) of a brief intervention

- **Ask** about tobacco use.
- **Advise** to quit.
- **Assess** willingness to make a quit attempt.
- **Assist** in quit attempt.
- **Arrange** followup.

211.09

Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence:2008 Update. Clinical Practice Guideline. Rockville,MD: U.S. Department of Health and Human Service. May 2008.

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## Ask

- Identify and document tobacco use status for every patient at every visit.
- Expand the vital signs to include tobacco use, or use alternative universal identification system.

## Advise

- Clear – “It is important that you quit smoking now, and I can help you.” “Occasional or light smoking is still dangerous.”

## Advise

- Strong – “As your clinician, I need you to know that quitting smoking is the most important thing you can do to protect your health now and in the future. The clinic staff and I will help you.”

## Advise

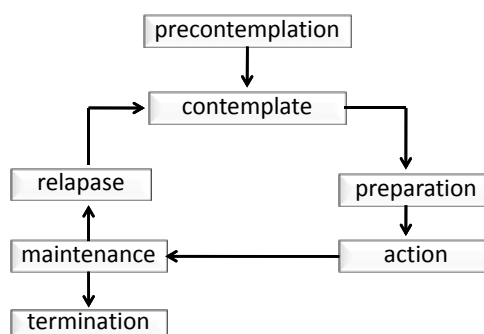
- Personalized- Tie tobacco use to symptoms and health concerns, and/or its social and economic costs, and/or the impact of tobacco use on children and others in the household.

## Assess

Assess patient’s willingness to quit:

“Are you willing to give quitting a try?”

## Stage of change



## Assist

- Help the patient with a quit plan.
- Recommend the use of approved medication.
- Provide practical counseling (problem solving /skills training)

## Arrange

- **Timing** : Follow up contact should begin soon after the quit date , preferably during the first week.  
A second follow up contact is recommend within the first month.  
Schedule further follow up contact as indicated.

## Arrange

- Action during follow up contact:  
For all patients, identify problems already encountered and anticipate challenges in the immediate future.  
Assess medication use and problems.  
Remind patients of quit line support.

## Clinical guidelines for prescribing medication for treating tobacco use and dependence

- All smokers trying to quit should be offered medication, except when contraindicated or specific populations for which there is insufficient evidence of effectiveness.

## What are the first-line medications recommended in this Guideline update?

- Varenicline
- Bupropion SR
- Nicotine gum
- Nicotine patch
- Nicotine inhaler
- Nicotine lozenge
- Nicotine nasal spray

## Second-line medications

- Nortriptyline
- clonidine

## Clinical use of varenicline

- A first-line medication
- Cardiovascular diseases – Not contraindicated
- Use with caution in patients with significant kidney disease (Cr clearance < 30 ml/min) or who are on dialysis.

## Clinical use of varenicline

- May experience impairment of the ability to drive or operate heavy machinery.
- Depressed mood, agitation, changes in behavior, suicidal ideation, and suicide have been reported in patients attempting to quit smoking

## Clinical use of varenicline

- Side effects – Nausea, trouble sleeping, abnormal/vivid/strange dreams.
- Start varenicline 1 week before the quit date at 0.5 mg once daily for 3 days, followed by 0.5 mg twice daily for 4 days, followed by 1 mg twice daily for 3 months.



## Clinical use of bupropion SR

- A first-line medication
- Cardiovascular diseases – Generally well-tolerated; occasional reports of hypertension.
- Side effects – insomnia (35-40%) and dry mouth (10%)

## Clinical use of bupropion SR

- Bupropion SR is contraindicated in individuals who have a history of seizures or eating disorders, who are taking another form of bupropion, or who have used an MAO inhibitor in the past 14 days.



## Clinical use of bupropion SR

- Should begin treatment 1-2 weeks before quit smoking.
- Begin with a dose of 150 mg every morning for 3 days, then increase to 150 mg twice daily for 7 – 12 weeks.
- For long-term therapy, consider use of bupropion SR 150 mg for up to 6 months post quit.

## Clinical use of nicotine gum

- A first-line medication.
- NRT is not an independent risk factor for acute myocardial events.
- Should be used with caution in the immediate(within 2 weeks) post myocardial infarction period, those with serious arrhythmias, and those with unstable angina pectoris.

## Clinical use of nicotine gum

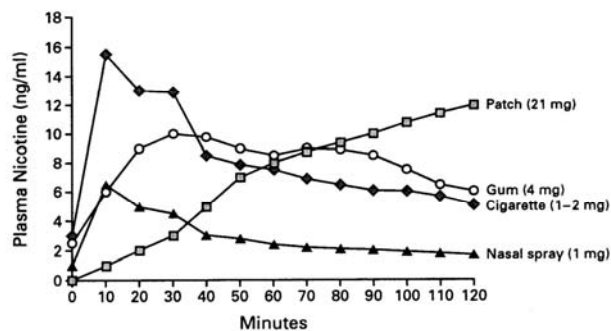
- Common side effects include mouth soreness, hiccups, dyspepsia, and jaw ache.
- The 2- mg gum is recommended for patients smoking less than 25 cigarettes per day.
- The 4- mg gum is recommended for patients smoking 25 or more cigarettes per day.

## Clinical use of the nicotine patch

- A first-line medication
- NRT is not an independent risk factor for acute myocardial events.
- Should be used with caution in the immediate(within 2 weeks) post myocardial infarction period, those with serious arrhythmias, and those with unstable angina pectoris.

## Clinical use of nicotine patch

- Up to 50% of patients will experience a local skin reaction.
- Other side effects – insomnia and/or vivid dreams.
- Treatment of 8 weeks or less has been shown to be as efficacious as longer treatment periods.



**Figure 2.** Plasma Nicotine Levels after a Smoker Has Smoked a Cigarette, Received Nicotine Nasal Spray, Begun Chewing Nicotine Gum, or Applied a Nicotine Patch.

The amount of nicotine in each product is given in parentheses. The pattern produced by the use of the nicotine inhaler (not shown) is similar to that for nicotine gum. Modified from Garrett et al.<sup>12</sup>

## Clinical use of nortriptyline

- A second – line medication.
- Most commonly reported side effects include sedation, dry mouth (64-78%), blurred vision (16%), urinary retention, lightheadedness (49%), and shaky hands (23%).
- May impair the mental and/or physical abilities.

## Clinical use of nortriptyline

- Because of the risk of arrhythmias and impairment of myocardial contractility, use with caution in patients with cardiovascular disease.
- Do not co-administer with MAO inhibitors.

## Clinical use of nortriptyline

- Initiated treatment at a dose of 25 mg /day, increasing gradually to a target dose of 75–100 mg/day.
- Therapy is initiated 10-28 days before the quit date to allow nortriptyline to reach steady stage at the target dose.
- Duration of treatment approximately 12 weeks.

## Clinical use of nortriptyline

- Overdose may produce severe and life-treating cardiovascular toxicity, as well as seizures and coma.

## For the patient unwilling to quit

- Promoting the motivation to quit.
- Focus on exploring a tobacco user’s feelings, beliefs, ideas, and values regarding tobacco use in an effort to uncover any ambivalence about using tobacco.

## Motivational interviewing strategies

- Express empathy
- Develop discrepancy
- Roll with resistance
- Support self-efficacy

## Express empathy

- Use open-ended questions to explore
- Use reflective listening to seek shared understanding
- Normalize feelings and concerns
- Support the patient's autonomy and right to choose or reject change

## Develop discrepancy

- Highlight the discrepancy between the patient's present behavior and expressed priorities, values, and goals.
- Reinforce and support "change talk" and "commitment" language.
- Build and deepen commitment to change.

## Roll with resistance

- Back off and use reflection when the patient expresses resistance
- Express empathy
- Ask permission to provide information

## Support self-efficacy

- Help the patient to identify and build on past success.
- Offer options for achievable small steps toward change.

## Enhancing motivation to quit tobacco - the "5R's"

- Relevance
- Risks
- Rewards
- Roadblocks
- Repetition

## For the patient who has recently quit

- Congratulations on any success and strong encouragement to remain abstinent.
- Identify a problem that negatively affects health or quality of life.

Meta-analysis(2000): Effectiveness of and estimated abstinence rates for various intensity levels of session length (n=43 studies)

Level of contact	Number of arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
No contact	30	1.0	10.9
< 3 minutes	19	1.3(1.01-1.6)	13.4 (10.9-16.1)
3-10 minutes	16	1.6(1.2-2.0)	16.0 (12.8-19.2)
>10 minutes	55	2.3(2.0-2.7)	22.1 (19.4-24.7)

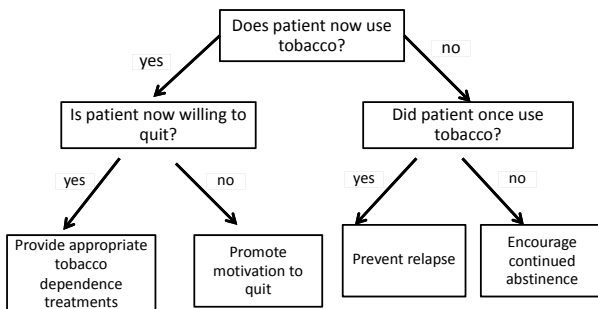
Fiore MC, Janz CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. May 2008.

Meta-analysis(2008): Effectiveness of and estimated abstinence rate for quitline counseling and medication compared to medication alone (n = 6 studies)

Intervention	Number Of arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Medication alone	6	1.0	23.2
Medication and quitline counseling	6	1.3 (1.1-1.6)	28.1 (24.5-32.0)

211.09 Fiore MC, Janz CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. May 2008.

### Algorithm for treating tobacco use



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## การดำเนินงานเรื่องการเลิกสูบบุหรี่ ในคลินิกรักษาสุขภาพ

ภาควิชาเวชศาสตร์ครอบครัว  
คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี

วิภา พินิจวัฒนา  
พยาบาลประจำคลินิกรักษาสุขภาพ

25.09.09 71

## คลินิกรักษาสุขภาพ

### วัตถุประสงค์

1. ให้บริการสุขภาพเพื่อปรับเปลี่ยนพฤติกรรมผู้ป่วย 4 ด้าน

1. Smoking
2. Insomnia
3. Obesity
4. Sedentary life style



## คลินิกรักษาสุขภาพ

### วัตถุประสงค์

2. เป็นที่เรียนรู้ คุณาน และฝึกปฏิบัติ ในการดูแลผู้ป่วย เพื่อปรับเปลี่ยนพฤติกรรม ของ แพทย์ประจำบ้าน เวชศาสตร์ครอบครัว และ นักศึกษานานาชาติ

เวลาให้บริการ วันพฤหัสบดี 13.00 – 15.00 น.

## คลินิกรักษาสุขาภาพ

- ผู้ร่วมทีม
1. แพทย์
  2. พยาบาล
  3. นักจิตวิทยา
  4. ผู้ปฏิบัติการพยาบาล
  5. นักกิจกรรมบำบัด



- ทีม Consult
1. นักสังคมสงเคราะห์
  2. ทีมเยี่ยมบ้าน

## Smoking

### วัตถุประสงค์

ให้บริการผู้ป่วยที่ต้องการเลิกสูบบุหรี่ โดยการปรับเปลี่ยนพฤติกรรม (BI)

## Smoking

### กลุ่มเป้าหมาย

1. ผู้ป่วยที่แพทย์เจ้าของไข้ส่งมาปรึกษาเรื่องการเลิกบุหรี่  
จาก - หน่วยผู้ป่วยนอกเวชศาสตร์ครอบครัว  
- หน่วยผู้ป่วยนอกอื่นๆ
2. ผู้ป่วยที่ต้องการเลิกสูบบุหรี่

## Smoking

### วิธีดำเนินการ

1. สร้างสัมพันธภาพ
2. อธิบายให้ผู้ป่วยทราบถึง วัตถุประสงค์ของคลินิก รักษาสุขาภาพ วิธีดำเนินการ การเปิดให้บริการ และ ให้ผู้ป่วยแสดงความต้องการเข้ารับบริการที่คลินิก
3. ชักประวัติ ชั่ง น้ำหนัก วัดส่วนสูง

## Smoking

### วิธีดำเนินการ

4. ประเมินระดับการติดยาโคติน
5. ประเมินระดับ การเปลี่ยนแปลงพฤติกรรม
6. ชักประวัติเกี่ยวกับการสูบบุหรี่
7. พบแพทย์

## Smoking

### วิธีดำเนินการ

8. พบนักจิตวิทยาในรายที่มีปัญหาซับซ้อน
9. ประชุมอภิปราย ปัญหาผู้ป่วยแต่ละราย แบบสหวิชาชีพ
10. ติดตามผู้ป่วยอย่างสม่ำเสมอ

## Smoking

### ผลการดำเนินการ

#### จำนวนผู้ป่วย

ที่ส่งเข้าคลินิก เรื่องต้องการเลิกบุหรี่ 74 ราย

ไม่มาตามนัด 35 ราย (47.3%)

มารับบริการ 39 ราย (52.7%)

## Smoking

### ผลการดำเนินการ

#### ลักษณะทั่วไป

เพศชาย 94.9% อายุเฉลี่ย 52 ปี

ส่วนใหญ่ รับราชการ 41%

มีโรคประจำตัว DLD 33.3%, DM 28.2%, HT 25.6%

ส่วนใหญ่ เคยลองเลิกสูบบุหรี่มาแล้ว 87.2%

## Smoking

### ผลการดำเนินการ

#### การประเมินระดับการติดนิโคติน (Fagerstrom test)

0 - 2 คะแนน ติดนิโคตินน้อย 17.9%

3 - 4 คะแนน ติดนิโคตินปานกลาง 30.8%

5 - 10 คะแนน ติดนิโคตินรุนแรง 51.3%

## Smoking

### ผลการดำเนินการ

#### Stage of change (ครั้งแรก)

Precontemplation 17.9%

Contemplation 5.1%

Preparation 76.9%

Action -%

Maintenance -%

## Smoking

### ผลการดำเนินการ

#### Treatment

Brief advice 59%

Brief advice + Drug 41%

## Smoking

### Stage of change (Follow up)

Precontemplation 15.4%

Contemplation -%

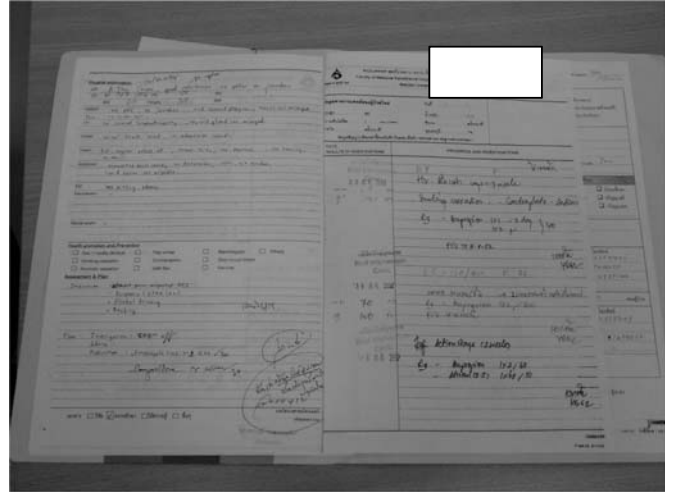
Preparation 5.1%

Action 30.8%

Maintenance 5.1%

สูญเสียดัง 23.1%

Loss Follow up 20.5%



**របៀបវារៈសម្រាប់ការពិនិត្យ**

ជំងឺវិកលចរិត គឺជាជំងឺស្រាប់តែមានលក្ខណៈ  
 មិនអាចទប់ទល់បាន ដោយការព្យាបាលប្រចាំថ្ងៃ ដោយធានា  
 ប្រសិនបើមិនមានការ គ្រប់គ្រង ឬ មិនបានប្រើប្រាស់ថ្នាំព្យាបាល

1. ត្រូវមានការពិនិត្យជាប្រចាំ
  - ១ ដងក្នុងមួយខែ ( ១ ពេញខែ )
  - ២ ដងក្នុងមួយខែ ( ២ ពេញខែ )
  - ៣ ដងក្នុងមួយខែ ( ៣ ពេញខែ )
  - ៤ ដងក្នុងមួយខែ ( ៤ ពេញខែ )
2. ត្រូវមានការពិនិត្យប្រសិនបើមានការប្រែប្រួល
  - ១ ដងក្នុងមួយខែ ( ១ ពេញខែ )
  - ២ ដងក្នុងមួយខែ ( ២ ពេញខែ )
  - ៣ ដងក្នុងមួយខែ ( ៣ ពេញខែ )
  - ៤ ដងក្នុងមួយខែ ( ៤ ពេញខែ )
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  - ១ ដងក្នុងមួយខែ ( ១ ពេញខែ )
  - ២ ដងក្នុងមួយខែ ( ២ ពេញខែ )
4. ត្រូវមានការពិនិត្យប្រសិនបើមានការប្រែប្រួល
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5. ត្រូវមានការពិនិត្យប្រសិនបើមានការប្រែប្រួល
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6. ត្រូវមានការពិនិត្យប្រសិនបើមានការប្រែប្រួល
  - ១ ដងក្នុងមួយខែ ( ១ ពេញខែ )
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រយៈពេលពិនិត្យ ១ ដងក្នុងមួយខែ  
 ឆ្នាំ ១ ដង

រយៈពេលពិនិត្យ ១ ដងក្នុងមួយខែ  
 ឆ្នាំ ១ ដង







*Thank you  
for your attention*

