MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Tobacco Use Disorder

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Disclosure

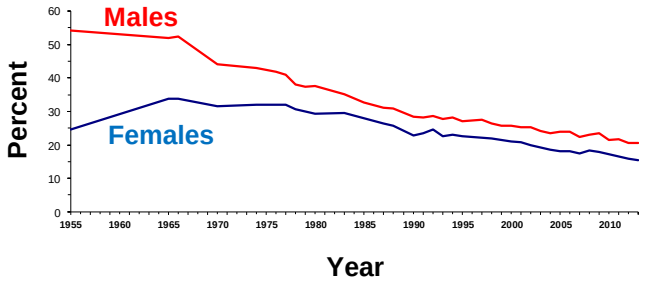
Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Case: Nancy D.

- 55-year-old woman with right breast cancer, s/p chemoradiation and mastectomy with history of HTN, AUD in early remission, and underlying depression.
- Smokes about a ½ pack of cigarettes per day.
- Expresses interest in stopping when asked but reluctant as 'nothing has ever worked.'
- Has tried nicotine patch, nicotine lozenges, and trial of bupropion.
- Tells you she has heard about varenicline, but her other provider was concerned about her depression and potential side effects.
- She does not feel confident that she can stop.

Smoking: Scope of the Problem

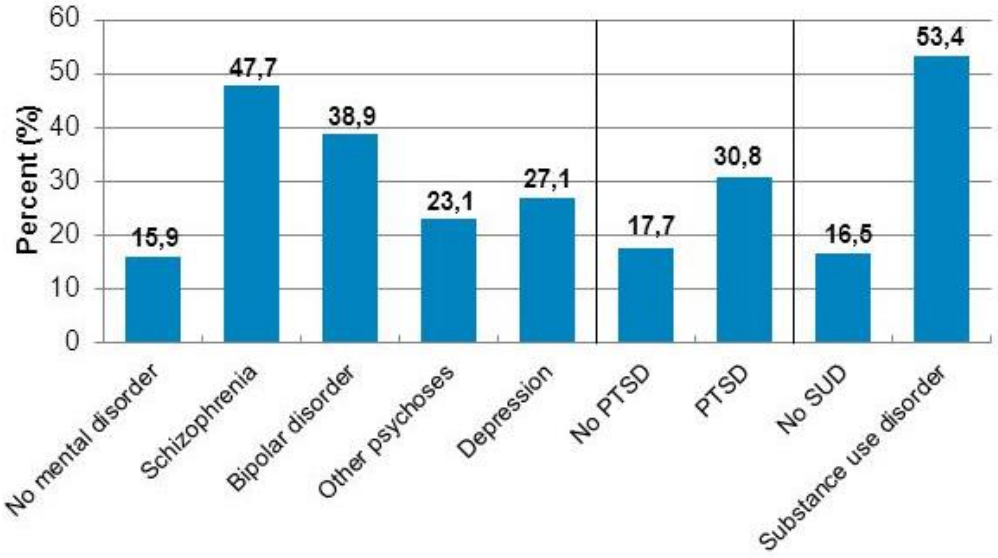
Trends in cigarette smoking among adults, 1955-2013



CDC: 1955 Current Population Survey; 1965 – 2013 NHIS.

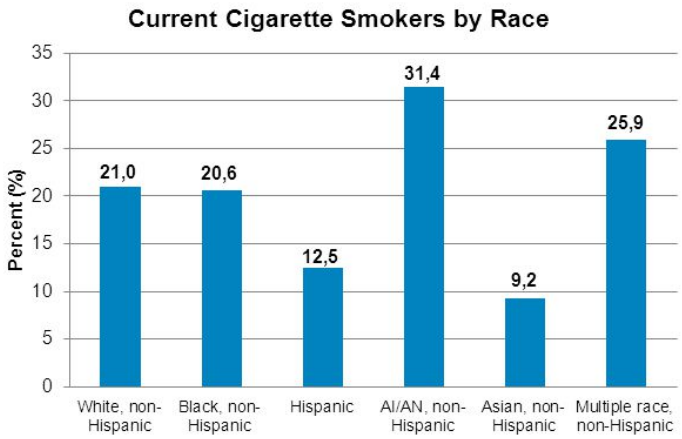
- Leading preventable cause of death worldwide
- In the U.S., affects 45 million adults (18%)
- Overall decrease in smoking rates over time, and patterns are changing (lower consumption, combinations of products)
- Higher prevalence of smoking in pts with a MH or SUD diagnosis

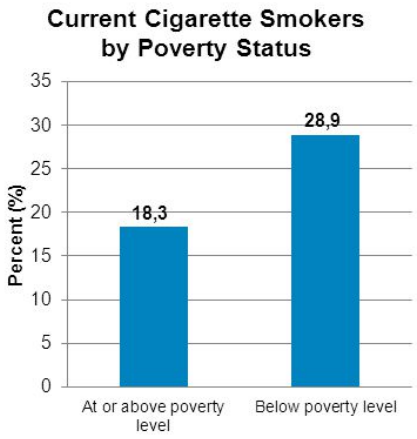
Current smokers– VA system



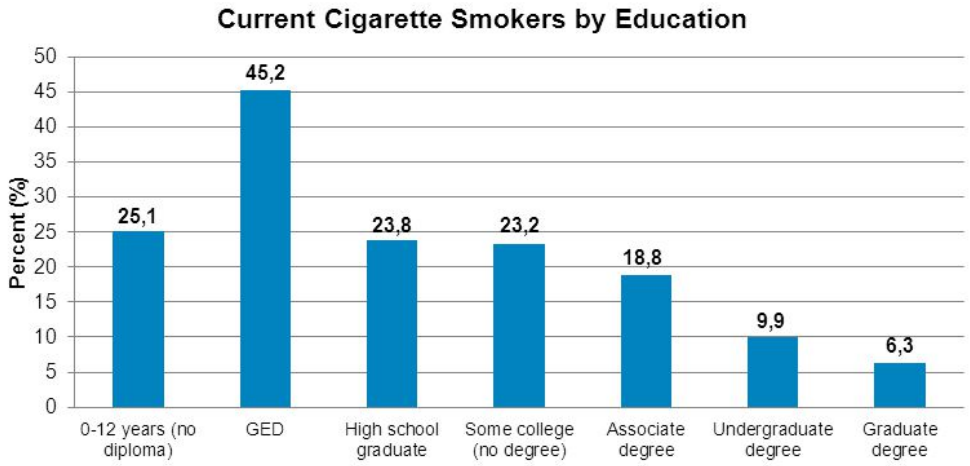
Duffy SA et al. (2012)
Psychiatric Serv. 63:325.

Smoking: Scope of the Problem





- Smoking rates vary by race / ethnicity and poverty status



- Prevalence is higher in those with lower educational attainment

CDC (2011)
MMWR 60: 1207.

Smoking: Scope of the Problem

Annual U.S. Deaths Attributable to Smoking, 2005 - 2009

		Percent of all smoking-attributable deaths
Cardiovascular & metabolic diseases	160,600	33%
Lung cancer	130,659	27%
Pulmonary diseases	113,100	23%
Second-hand smoke	41,280	9%
Cancers other than lung	36,000	7%
Other	1,633	<1%

TOLL: >480,000 deaths annually, $130 billion/yr in added medical costs

U.S. Department of Health and Human Services (2014) The Health Consequences of Smoking– 50 Years of Progress: A report of the Surgeon General.

Smoking Cessation: Benefits

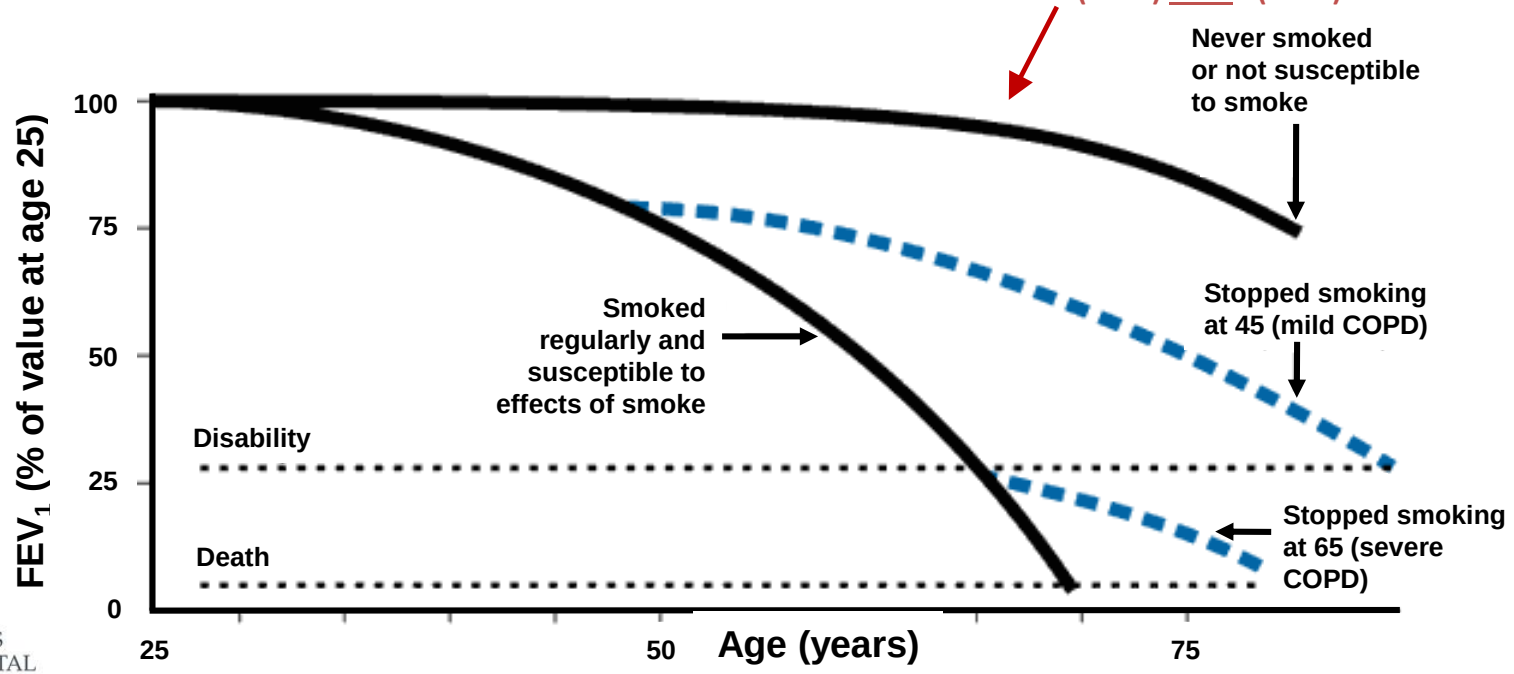
- 69% of smokers want to quit
- 53% of smokers have tried in the past year
- Only 6% attain abstinence at one year, and 50% relapse within 1 week
- Success of quitting lower with concurrent SUD or psychiatric disorder

HOWEVER:

- Cessation benefits all smokers– regardless of length of smoking, level of illness, comorbidity, or age

Slowing the decline of pulmonary function

Fletcher and Peto (1977) BMJ 1 (6077): 1645.

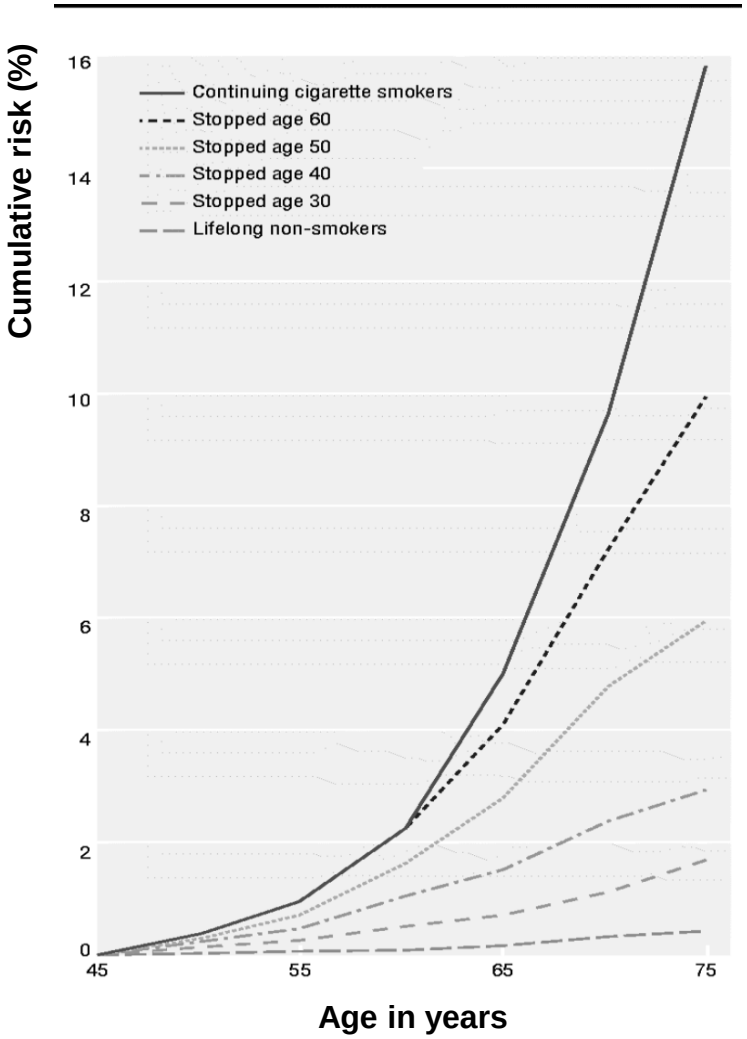


COPD = chronic obstructive pulmonary disease

Smoking Cessation: Benefits

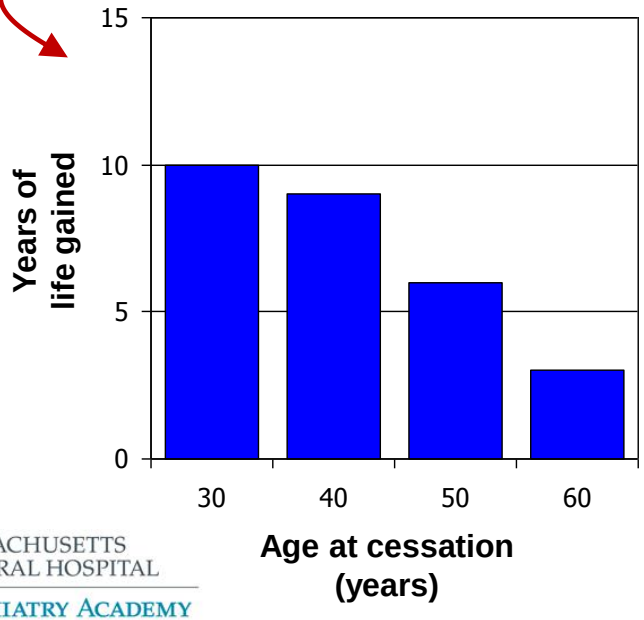
Reduction in cumulative risk of death from lung cancer in men

Peto (2000) *BMJ* 321 (7257): 323.



50-year follow-up of 34,000 British male physicians

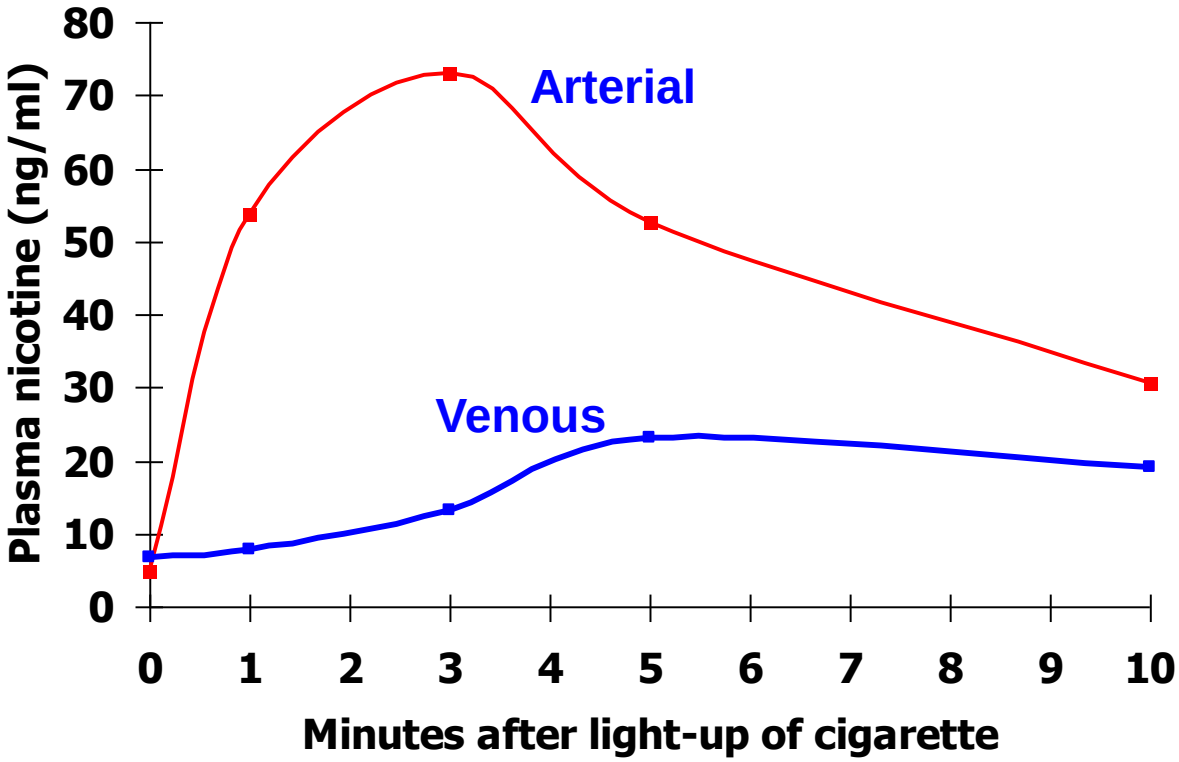
Doll et al. (2004) *BMJ* 328 (7455): 1519.



Nicotine Pharmacology

- Readily absorbed through intact skin
- Well absorbed in the small intestine but has low bioavailability (20-45%) due to first-pass hepatic metabolism
- Carried in tar droplets and rapidly absorbed across respiratory epithelium
  - Significant proportion lipophilic at pH 7.4
  - Large alveolar surface area
  - Extensive capillary system in lung

Nicotine Pharmacology

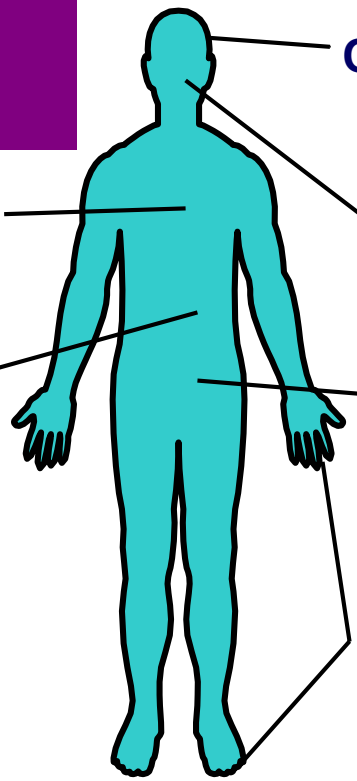


Nicotine reaches the brain within 10–20 seconds.

Hennngfield et al. (1993) *Drug and Alcohol Dependence* 33: 23.

Nicotine Pharmacology

Nicotine binds to receptors in the brain and other sites in the body.



Central nervous system

Exocrine glands

Adrenal medulla

Peripheral nervous system

Cardiovascular system

Gastrointestinal system

Other:

- **Neuromuscular junction**
- **Sensory receptors**
- **Other organs**

Nicotine has predominantly stimulatory effects.

Nicotine Pharmacology

Central nervous system

- Pleasure
- Arousal, enhanced vigilance
- Improved task performance
- Anxiety relief

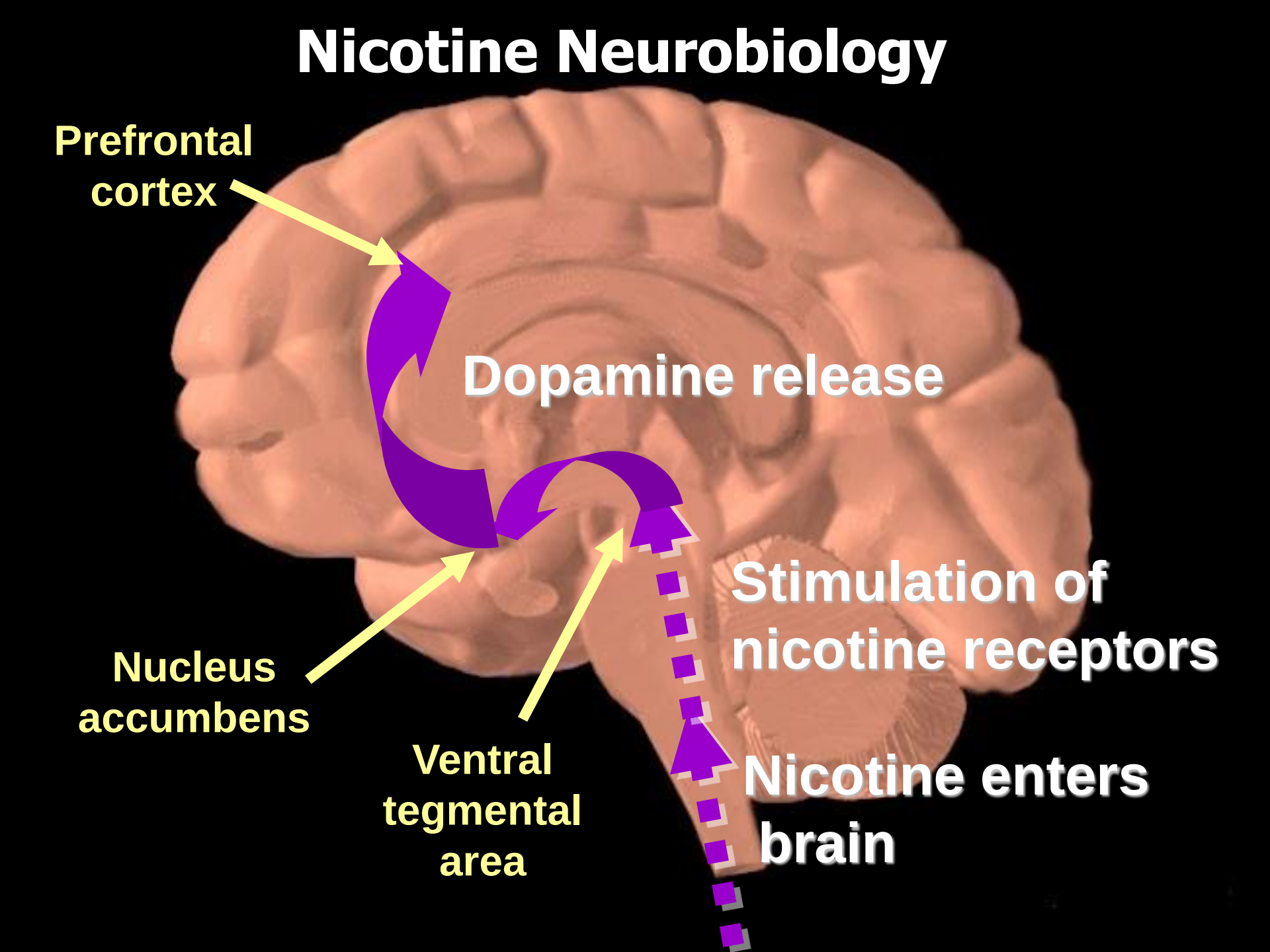
Other

- Appetite suppression
- Increased metabolic rate
- Skeletal muscle relaxation

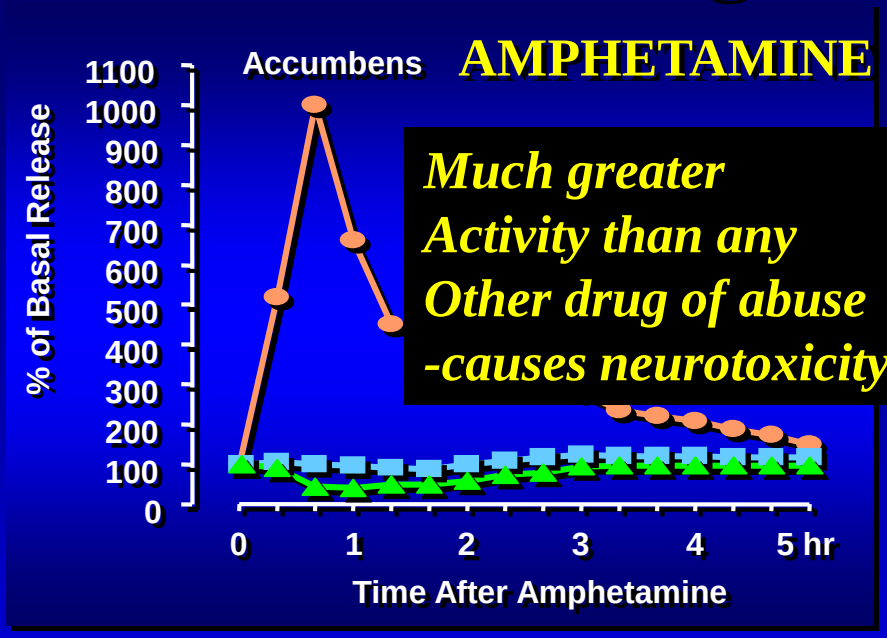
Cardiovascular system

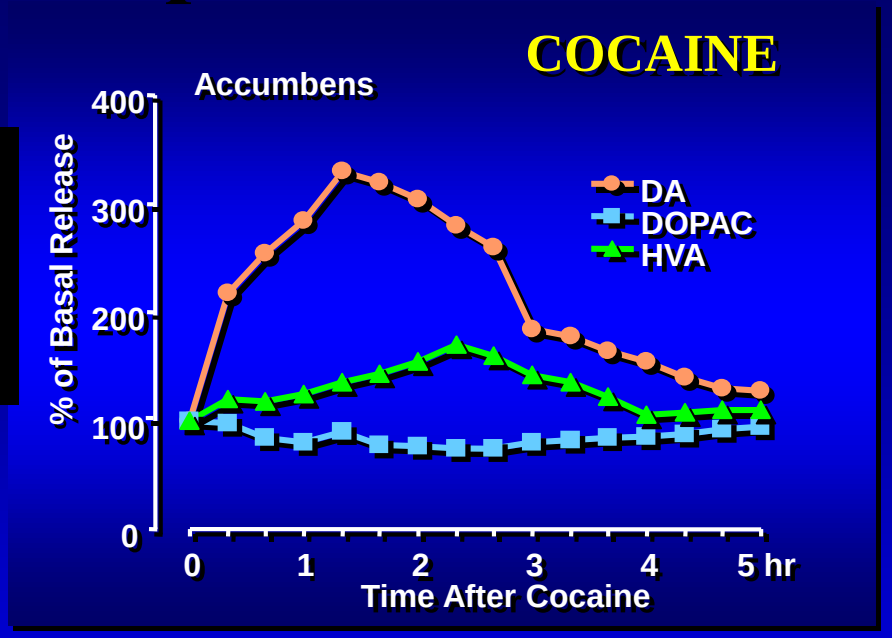
- ↑ Heart rate
- ↑ Cardiac output
- ↑ Blood pressure
- Coronary vasoconstriction
- Cutaneous vasoconstriction

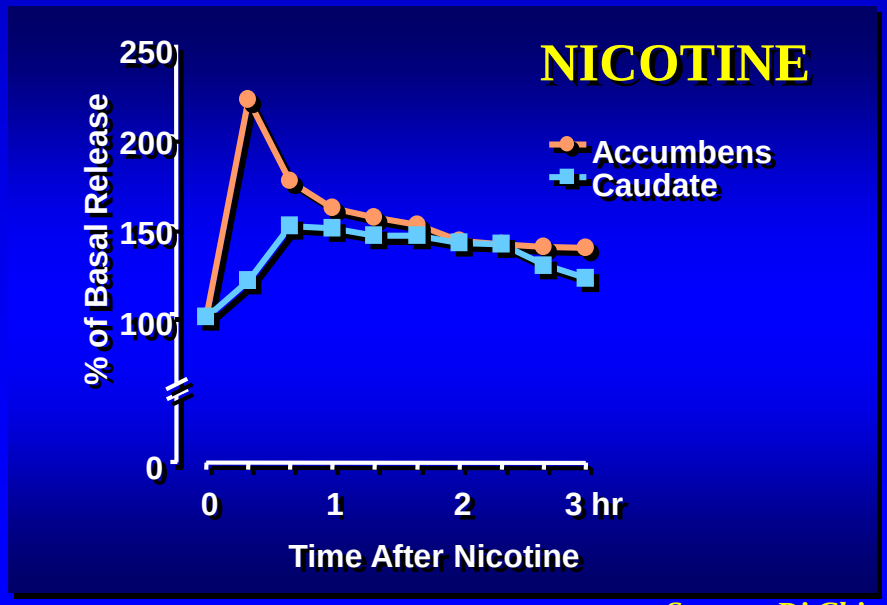
Nicotine Neurobiology

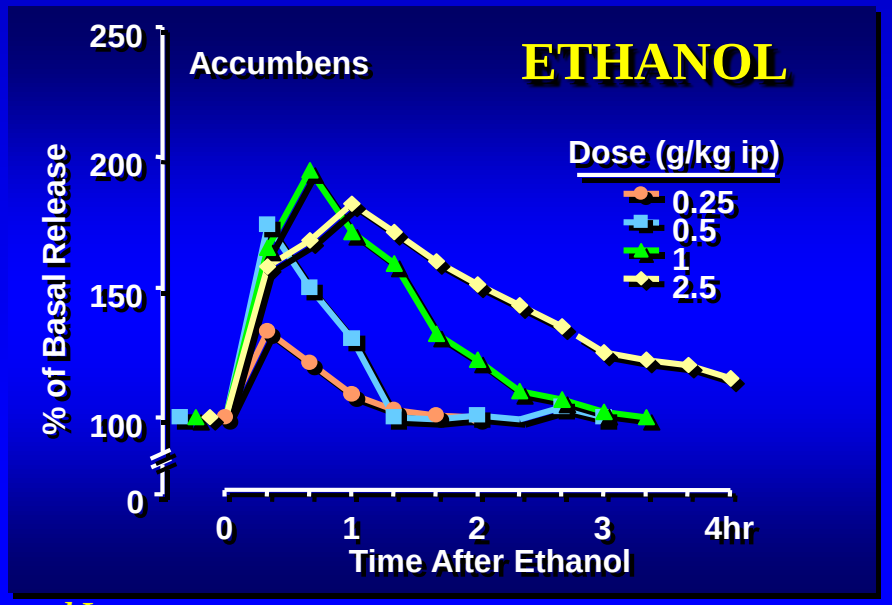


Effects of Drugs on Dopamine Release









Source: Di Chiara and Imperato

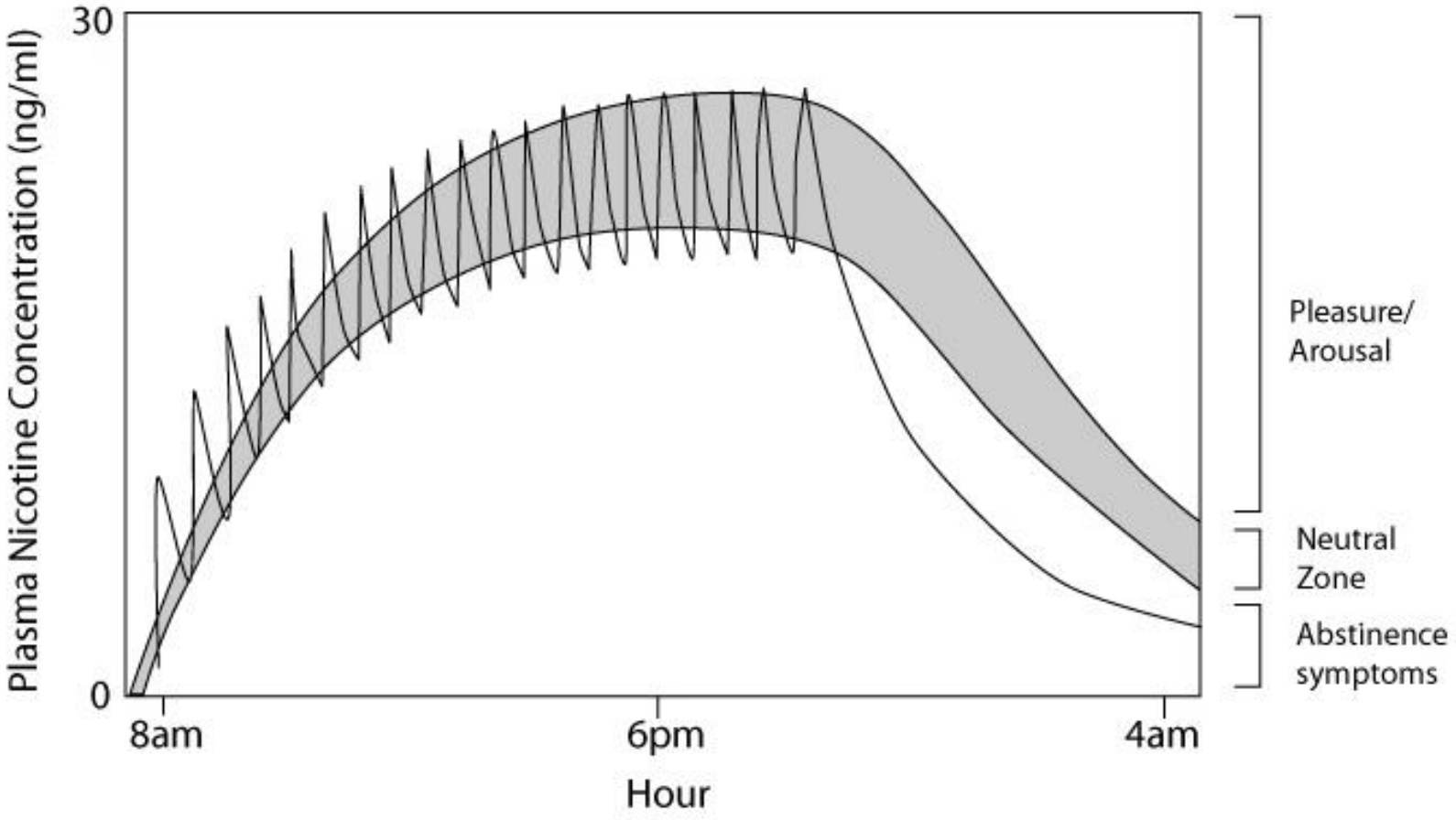
Nicotine Withdrawal

- Irritability/frustration/anger
- Anxiety
- Difficulty concentrating
- Restlessness/impatience
- Depressed mood/depression
- Insomnia
- Impaired performance
- Increased appetite/weight gain
- Cravings

Most symptoms manifest within the first 1–2 days, peak within the first week, and subside within 2–4 weeks.

Source: Hughes (2007) Nicotine Tob Res 9: 315.

Cycle of Nicotine Dependence



Benowitz (1992) *Med Clin N Am* 2: 415.

Factors Affecting Nicotine Use

Individual

- Sociodemographics
- Genetic predisposition
- Coexisting medical conditions

Physiological

- Alleviation of withdrawal symptoms
- Weight control
- Pleasure, mood modulation

Environment

- Tobacco advertising
- Conditioned stimuli
- Social interactions

Proven Smoking Cessation Therapies

Though expensive, hiring a professional actor dressed as death to stalk his every move finally broke Ted of his smoking addiction.

Proven Smoking Cessation Therapies

Two modalities with a strong evidence base

Behavioral Support

- CBT / motivational enhancement
- Brief counseling by clinicians
- Phone-based counseling– e.g., the system of state-based quit lines (1-800-QUIT-NOW)
- Text and internet-based counseling methods

NOT (yet) well supported:

- Hypnosis
- Acupuncture
- Contingency management

Pharmacotherapy

- Nicotine replacement
- Bupropion
- Varenicline

- Nortriptyline
- Clonidine

NOT (yet) as well supported:

- SSRIs
- Anxiolytics
- E-cigarettes (1st, 2nd, 3rd generation)
- Nicotine vaccine

Proven Smoking Cessation Therapies

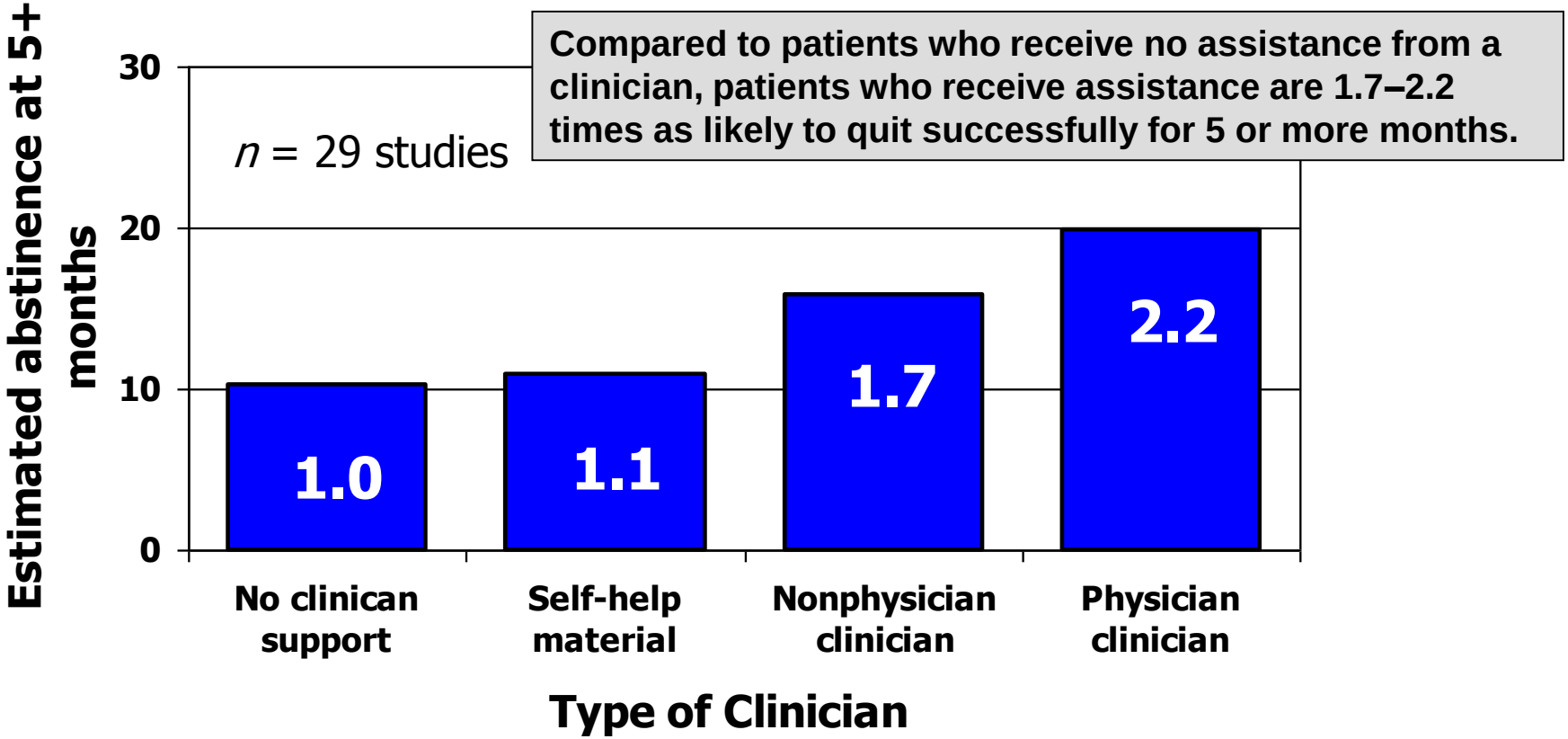
Summary of treatment efficacy for behavioral and pharmacologic methods

Source: Rigotti (2012) JAMA 308: 1573.

Table 1. Efficacy of Methods Used to Treat Tobacco Dependence: Meta-analyses From the Cochrane Database of Systematic Reviews[a]

Method	Nonpharmacologic Methods vs Minimal or Usual Care, Risk Ratio (95% CI)	No. of Trials in Meta-analysis
Nonpharmacologic methods		
Smoking cessation counseling		
Individual	1.39 (1.24-1.57)	22
Group	1.98 (1.60-2.46)	13
Telephone quit line	1.37 (1.26-1.50)	9
Physician intervention		
Brief advice to quit vs no advice or usual care	1.66 (1.42-1.94)	17
Brief counseling vs		
No advice or usual care	1.84 (1.60-2.13)	11
Brief advice	1.37 (1.20-1.56)	
	Pharmacologic Methods vs Placebo or No Treatment	
Pharmacologic methods		
First-line drugs[b]		
Bupropion SR	1.69 (1.53-1.85)	36
Varenicline	2.27 (2.02-2.55)	14
Nicotine replacement		
Patch	1.66 (1.53-1.81)	41
Gum	1.43 (1.33-1.53)	53
Lozenge	2.00 (1.63-2.45)	6
Inhaler	1.90 (1.36-2.67)	4
Nasal spray	2.02 (1.49-3.73)	4
Second-line drugs[c]		
Nortriptyline[d]	2.03 (1.48-2.78)	6
Clonidine [e]	1.63 (1.22-2.18)	6

Effect of Provider Interventions



Fiore et al. (2008) Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: USDHHS, PHS.

A Frame for Intervention: The 5 A's

ASK

ADVISE

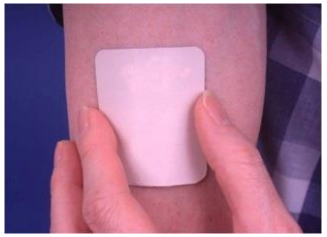
ASSESS

ASSIST

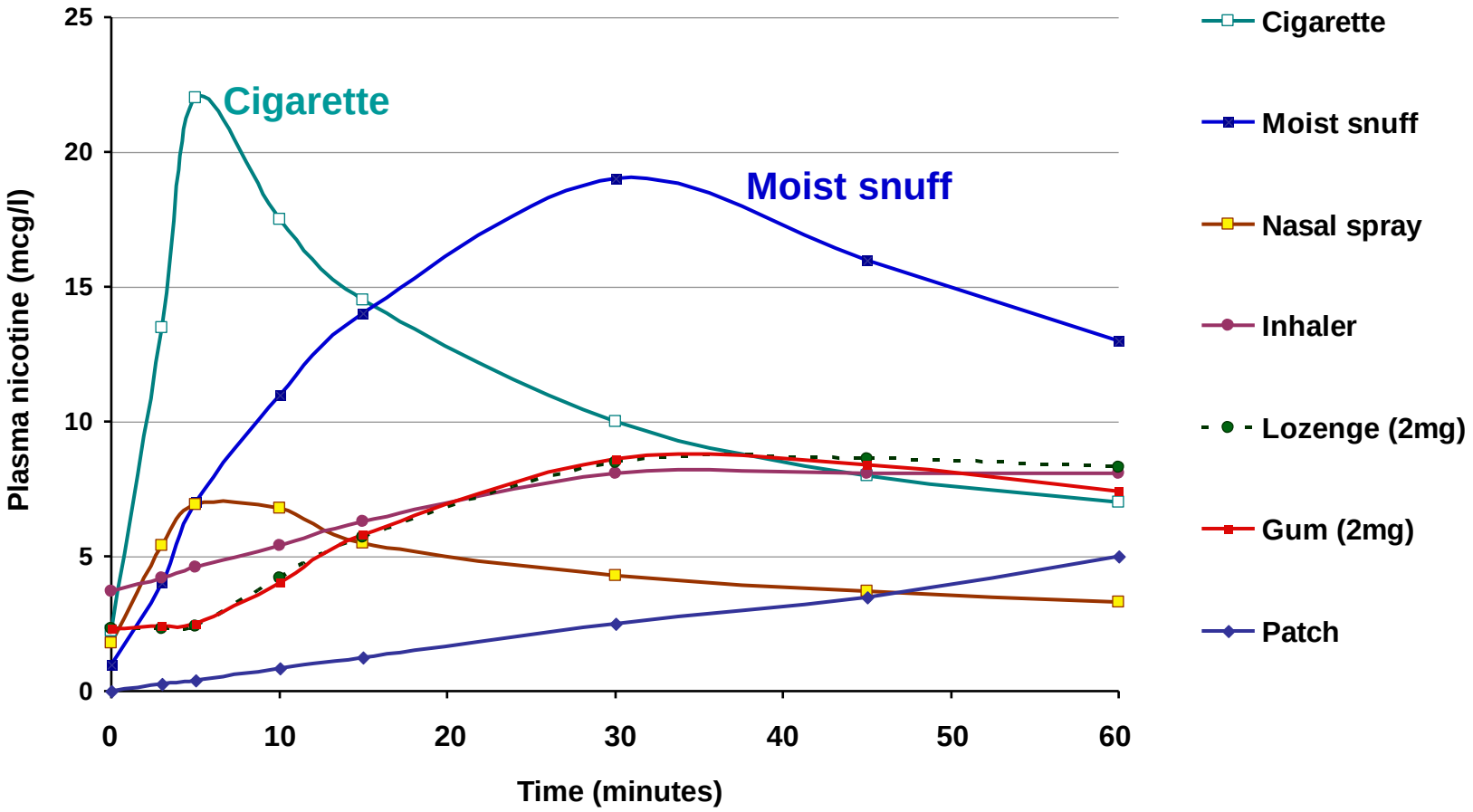
ARRANGE

Nicotine Replacement Therapy

- Three OTC options: patch, gum, lozenge.
- Two Rx-only options: oral inhaler, nasal spray
- Range for rate of onset is variable amongst them



Nicotine Replacement Therapy



Choi JH, Dresler CM, Norton MR, Strahs KR. (2003). *Nicotine Tob Res* 5:635–644.
Fant RV, Henningfield JE, Nelson RA, Pickworth WB. (1999). *Tob Control* 8:387–392.
Schneider NG, Olmstead RE, Franzon MA, Lunell E. (2001) *Clin Pharmacokinet* 40:661–684.

Nicotine Replacement Therapy

- Long-acting, slow onset
  - Skin patch
  - Steady nicotine level
  - Simple with good compliance
  - No user control
- Short-acting, faster onset
  - Oral: gum, lozenge, inhaler
  - Nasal: spray
  - User controls the dose
  - Greater fluctuations
- Newer ways to use old meds
  - Combine short and long-acting NRT
  - Treat longer to minimize relapse
  - Start NRT before quit talk
  - NRT or varenicline to decrease use in those not ready for full cessation
    - 'Reduce to quit'

Bupropion

- Atypical antidepressant that increases dopamine and norepinephrine levels in mesolimbic pathways.
- Improvement in cessation rates independent of antidepressant effects
- Usage: begin 1-2 weeks prior to quit date
- Side-effects: nausea, vivid / abnormal dreams, dry mouth
- Lowers seizure threshold (0.1% risk of seizure in smokers)
- May temporarily blunt cessation-related weight gain
- May be more effective in combination with NRT or varenicline

Varenicline

- Partial agonist at the α4β2 nicotinic acetylcholine receptor subtype (most important for nicotine dependence)
- Long-term efficacy superior to bupropion and NRT
- Usage: begin 1 week prior to quitting
- Side-effects: nausea, insomnia, vivid / abnormal dreams
- Post-marketing case reports of behavioral changes / suicidality, leading to a black box warning by the FDA
- However– a large 2016 trial (Anthenelli et al. (2016) *Lancet*) including patients with psychiatric comorbidity that showed no such negative effects
  - Black box warning removed in December of 2016

Pharmacologic Options: Summary

Drug	Dosing	Positives	Negatives
Nicotine patch	• 1 new patch daily • 21 mg for > 10 cigs/d • 14 mg for < 10 cigs/d • Taper after 4-6 wks	• Steady Nicotine level • Ease of use	• Nicotine released slowly, cannot be adjusted • Skin irritation, insomnia
Nicotine gum	• 1 piece per hour • 2 mg for < 25 cigs/d • 4 mg for > 25 cigs/d • < 24 pieces/d	• User controlled Nicotine level • Oral substitute for cigs	• Requires proper chewing technique (chew, pocket) • Can affect dental work • Can't mix with food/drink • Mouth irritation, jaw sx
Nicotine lozenge	• 1 piece every 1-2 hours • 2 mg for non-AM smokers • 4 mg for AM smokers	• User controlled • No effect on dentition	• Can't mix with food/drink • Hiccups, heartburn
Nicotine inhaler (10 mg cartridge)	• Inhale as needed • 6-10 cartridges/d	• User controlled • Oral substitute	• Device visible during use • Mouth / throat irritation
Nicotine nasal inhaler	• One puff in each nostril every 1-2 hours • < 40 applications/d	• User controlled • Most rapid Nicotine delivery	• Nasal irritation, sneezing, cough, eye tearing

Rigotti (2012) *JAMA* 308: 1573.

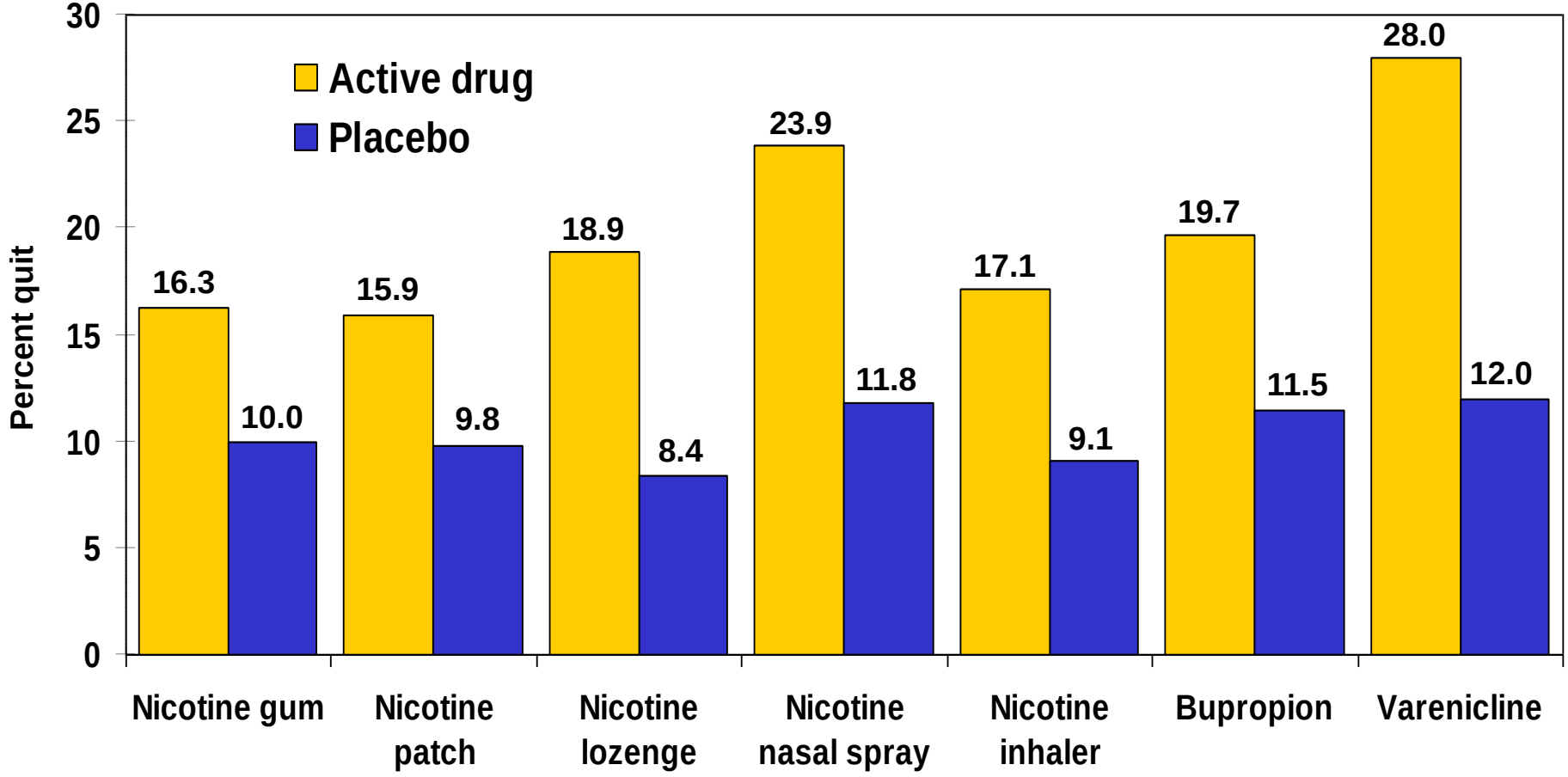
Pharmacologic Options: Summary

Drug	Dosing	Positives	Negatives
Bupropion SR	• 150 mg/d for 3 days, then 150 mg BID • Start 1 wk before quit date • Continue for 3-6 months	• Blunts cessation-related weight gain • Orally bioavailable	• Increased seizure risk • Concern re: psychiatric side-effects (boxed warning) • Insomnia, vivid dreams, dry mouth
Varenicline	• 0.5 mg/d for 3 days, then 0.5 mg BID for 4 days, then 1 mg BID • Start 1 wk before quit date • Continue for 3-6 months	• Dual action– both relieves withdrawal and blocks Nicotine-related reward • Orally bioavailable	• Concern re: psychiatric side-effects (boxed warning 2009, removed 2016) • FDA communication re: potential CV risk • Needs adjustment for renal dysfunction • Nausea, insomnia, vivid dreams

Rigotti (2012) *JAMA* 308: 1573.

Pharmacologic Options: Summary

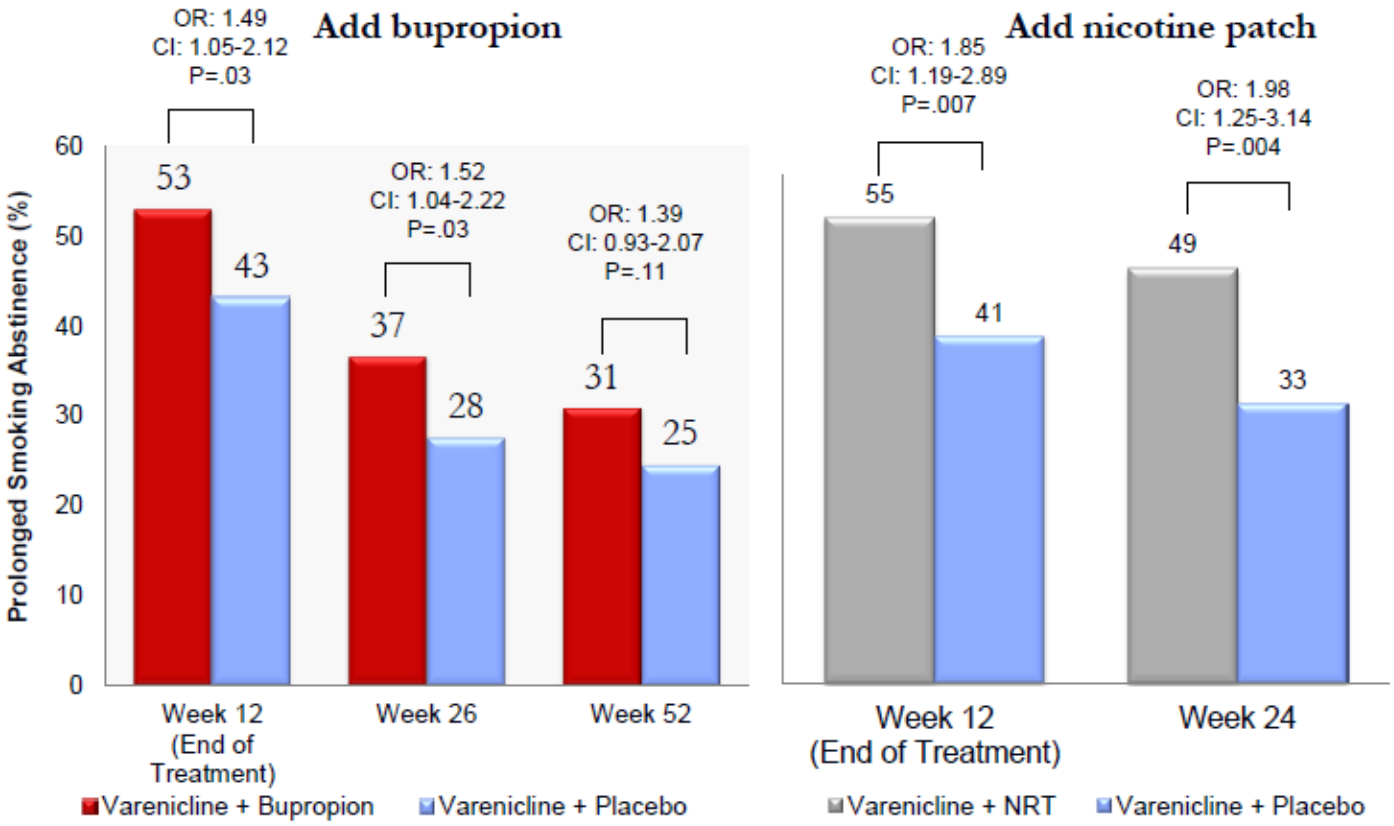
Long-term (> 6 month) quit rates for available therapies



Adapted from Cahill et al. (2012), Cochrane Database Syst Rev; Stead et al. (2012), Cochrane Database syst Rev; Hughes et al. (2014), Cochrane Database Syst Rev

Pharmacologic Options: Summary

Adding Bupropion or NRT to varenicline



Ebbert JO, et al. *JAMA*.2014;311(2):155–163.
Koegelenberg CF, et al. *JAMA*. 2014;312(2):155–161.

Pharmacologic Options: Summary

Triple Therapy?

- Methods:
  - 12-week, observational study exploring tolerability, via adverse events (AEs) elicited at each of nine phone assessments. Secondary outcomes included satisfaction rates, medication changes and self-reported quit rates at week 12.
  - Patients received varenicline 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 11 weeks, nicotine 21 mg for 8 weeks (starting on the TQD), followed by transdermal nicotine 14 mg for 2 weeks; followed by transdermal nicotine 7 mg for 2 weeks; nicotine mini lozenges (2 mg) used as needed for relief of withdrawal and craving, for 12 weeks (starting on the TQD), participants were urged to use at least four mini lozenges per day, but no more than 20 per day.

- Results:
  - 35 of 36 participants reported at least one AE. Insomnia (75%), abnormal dreams (72%) and nausea (64%) were most common. Most were mild to moderate. No deaths, hospitalizations, cardiovascular events or suicidality were reported. Six participants (17%) decreased the dose of at least one medication, 5 (14%) decreased the dose then discontinued at least one medication and 13 (36%) discontinued at least one medication without trying a lesser dose. Participants were highly satisfied with their medications, and 58% reported quitting at 12 weeks, with 38% reporting prolonged abstinence.

Berg, KM, et al. *J of Smoking Cessation* 2018; 13(3): 145-153

E-Cigarettes: Efficacy in Reducing Respiratory and Cardiovascular Risk

- Methods
  - Systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. Search using PubMed and Embase databases in September 2020 to identify epidemiological studies that compared odds of cardiovascular and respiratory outcomes among former smokers who transitioned to e-cigarettes relative to odds among current smokers not using e-cigarettes (current exclusive smokers). Studies that provided direct estimates of relevant odds ratios (ORs) were included. Studies where indirect estimates of relevant ORs could be calculated based on published results were also included. Two reviewers independently extracted data and conducted quality appraisals.
- Results
  - Six population-based studies with sample sizes ranging from 19,475 to 161,529 respondents met review inclusion criteria, five of which were cross-sectional and one longitudinal. Three studies reported respiratory outcomes and three reported cardiovascular outcomes. ORs of respiratory outcomes (including chronic obstructive pulmonary disease, chronic bronchitis, emphysema, asthma, and wheezing) in former smokers who transitioned to e-cigarettes versus current exclusive smokers were below 1.0, ranging from 0.58 (95%CI 0.36–0.94) to 0.66 (95%CI 0.50–0.87; all $p < 0.05$). All ORs for cardiovascular outcomes (including stroke, myocardial infarction, and coronary heart disease) did not differ significantly from 1.0
- Conclusion
  - Former smokers who transitioned to e-cigarettes showed ~ 40% lower odds of respiratory outcomes compared to current exclusive smokers. Switching from smoking to e-cigarette does not appear to significantly lower odds of cardiovascular outcomes. Since the utility of cross-sectional studies for causal inference remains limited, both randomized controlled trials and prospective cohort studies are needed to better evaluate contributions of e-cigarettes as harm reduction tools for smokers.

Goniewicz et al. *Harm Reduct J* 2020; 17:91

Randomized Trial of E-Cigarettes versus NRT

- Method:
  - Randomly assigned adults attending U.K. National Health Service stop-smoking services to either nicotine-replacement products of their choice, including product combinations, provided for up to 3 months, or an e-cigarette starter pack (a second-generation refillable e-cigarette with one bottle of nicotine e-liquid [18 mg per milliliter]), with a recommendation to purchase further e-liquids of the flavor and strength of their choice. Treatment included weekly behavioral support for at least 4 weeks. The primary outcome was sustained abstinence for 1 year, which was validated biochemically at the final visit. Participants who were lost to follow-up or did not provide biochemical validation were considered to not be abstinent. Secondary outcomes included participant-reported treatment usage and respiratory symptoms.
- Results:
  - A total of 886 participants underwent randomization. The 1-year abstinence rate was 18.0% in the e-cigarette group, as compared with 9.9% in the nicotine-replacement group (relative risk, 1.83; 95% confidence interval [CI], 1.30 to 2.58; P<0.001). Among participants with 1-year abstinence, those in the e-cigarette group were more likely than those in the nicotine-replacement group to use their assigned product at 52 weeks (80% [63 of 79 participants] vs. 9% [4 of 44 participants]). Overall, throat or mouth irritation was reported more frequently in the e-cigarette group (65.3%, vs. 51.2% in the nicotine-replacement group) and nausea more frequently in the nicotine-replacement group (37.9%, vs. 31.3% in the e-cigarette group). The e-cigarette group reported greater declines in the incidence of cough and phlegm production from baseline to 52 weeks than did the nicotine-replacement group (relative risk for cough, 0.8; 95% CI, 0.6 to 0.9; relative risk for phlegm, 0.7; 95% CI, 0.6 to 0.9). There were no significant between-group differences in the incidence of wheezing or shortness of breath.
- Conclusions:
  - E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support.

Hajek P et al. N Engl J Med 2019;380:629-637

Randomized Trial of E-Cigarettes versus NRT

Table 2. Abstinence Rates at Different Time Points and Smoking Reduction at 52 Weeks.*

Outcome	E-Cigarettes (N=438)	Nicotine Replacement (N=446)	Primary Analysis: Relative Risk (95% CI)†	Sensitivity Analysis: Adjusted Relative Risk (95% CI)
Primary outcome: abstinence at 52 wk — no. (%)	79 (18.0)	44 (9.9)	1.83 (1.30–2.58)	1.75 (1.24–2.46)‡
Secondary outcomes				
Abstinence between wk 26 and wk 52 — no. (%)	93 (21.2)	53 (11.9)	1.79 (1.32–2.44)	1.82 (1.34–2.47)§
Abstinence at 4 wk after target quit date — no. (%)	192 (43.8)	134 (30.0)	1.45 (1.22–1.74)	1.43 (1.20–1.71)¶
Abstinence at 26 wk after target quit date — no. (%)	155 (35.4)	112 (25.1)	1.40 (1.14–1.72)	1.36 (1.15–1.67)‡
Carbon monoxide–validated reduction in smoking of ≥50% in participants without abstinence between wk 26 and wk 52 — no./total no. (%)	44/345 (12.8)	29/393 (7.4)	1.75 (1.12–2.72)	1.73 (1.11–2.69)‖

* Abstinence at 52 weeks was defined as a self-report of smoking no more than five cigarettes from 2 weeks after the target quit date, validated biochemically by an expired carbon monoxide level of less than 8 ppm at 52 weeks. Abstinence between week 26 and week 52 was defined as a self-report of smoking no more than five cigarettes between week 26 and week 52, plus an expired carbon monoxide level of less than 8 ppm at 52 weeks. Abstinence at 4 weeks was defined as a self-report of no smoking from 2 weeks after the target quit date, plus an expired carbon monoxide level of less than 8 ppm at 4 weeks. Abstinence at 26 weeks was defined as a self-report of smoking no more than five cigarettes from 2 weeks after the target quit date to 26 weeks; there was no validation by expired carbon monoxide level.

† The analysis was adjusted for trial center only.

‡ The analysis was adjusted for trial center, marital status, age at smoking initiation, and score on the Fagerström Test for Cigarette Dependence.

§ The analysis was adjusted for trial center, age, score on the Fagerström Test for Cigarette Dependence, and age at smoking initiation.

¶ The analysis was adjusted for trial center, education level, partner who smokes (yes or no), and score on the Fagerström Test for Cigarette Dependence.

‖ The analysis was adjusted for trial center, sex, age, and partner who smokes (yes or no).

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Randomized Trial of E-Cigarettes versus NRT

Table 5. Respiratory Symptoms at Baseline and at 52 Weeks.*

Symptom	E-Cigarettes (N=315)		Nicotine Replacement (N=279)		Relative Risk (95% CI)†
	Baseline	52 Weeks	Baseline	52 Weeks	
	number (percent)				
Shortness of breath	120 (38.1)	66 (21.0)	92 (33.0)	64 (22.9)	0.9 (0.7–1.1)
Wheezing	102 (32.4)	74 (23.5)	86 (30.8)	59 (21.1)	1.1 (0.8–1.4)
Cough	173 (54.9)	97 (30.8)	144 (51.6)	111 (39.8)	0.8 (0.6–0.9)
Phlegm	137 (43.5)	79 (25.1)	121 (43.4)	103 (36.9)	0.7 (0.6–0.9)

* Symptoms were assessed by asking whether participants had the symptom (yes or no).
† Relative risk was calculated by means of logistic regression. Symptoms at 52 weeks were regressed onto trial group, with adjustment for baseline symptoms and trial center.

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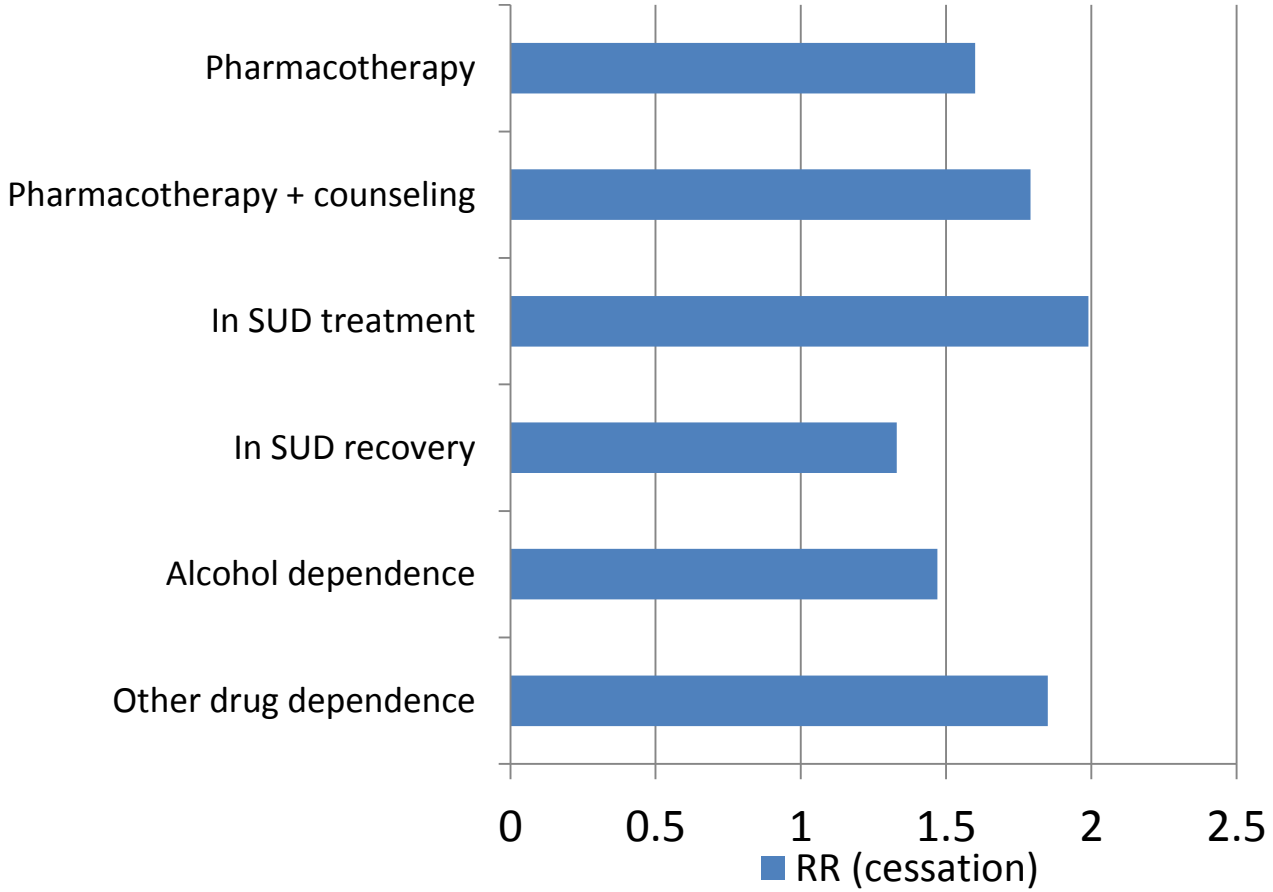
Smoking treatment in SUD patients

Meta-analysis of smoking treatment in 5700 pts with SUD



Appolonio et al. (2016) Cochrane Database of Systematic Reviews 11: CD010274.

Returning to our case…

- 55-year-old woman with right breast cancer, s/p chemoradiation and mastectomy, with history of HTN, AUD in early remission, and underlying depression.
  - Has history of breast cancer and HTN which can be leads into tobacco cessation discussion and carries two diagnoses (depression, AUD) with higher smoking rates

- Smokes 10-15 cigarettes per day.

  - Fits the trend toward lower total daily dosage (affects perceived risk)

Returning to our case…

- Expresses interest but that nothing has worked in the past
- Used a nicotine patch and lozenges for about 7 days, but discontinued when she smoked a cigarette
- While trying bupropion, she decreased cigarette intake however never stopped completely

  - Has only tried two FDA-approved therapies (one for only 1 week)
  - Has not tried combination therapies
  - Important to persist w/ NRT despite lapses
  - Did not set a clear quit date w/ use of NRT or bupropion

Returning to our case…

- Tells you she's heard that varenicline could be dangerous for him

  - No evidence that varenicline is dangerous in stable depression

- Says she does not feel confident in stopping

  - Good efficacy of treatment in patients in early or later recovery

Summary

- Cigarette smoking is the leading preventable cause of death worldwide, causing almost half a million deaths annually in the U.S.
- Quitting smoking causes improvements in health and survival regardless of when it occurs in the life / disease cycle
- Nicotine is rapidly absorbed into the body and quickly crosses the blood-brain barrier, where it readily activates the brain's addiction circuitry
- Treatment should accomplish the following:
  - Utilize both behavioral and pharmacologic treatments together
  - Combine different pharmacologic modalities when appropriate
  - Start BEFORE the quit date and continue despite setbacks
  - Proceed without hesitation for patients with psychiatric and substance use disorders