Smoking Cessation: An Update on Today’s Literature

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Disclosures

• I disclose that I am a Consultant for Boehringer Ingelheim, and a member of the Boehringer Ingelheim’s speaker’s bureau. My presentation will not include discussion of off-label or unapproved usage.

Tobacco Abuse

• Leading cause of preventable premature mortality worldwide
• 6 million deaths linked to tobacco annually
• 200,000 deaths in the U.S. annually
• 1 billion people worldwide continue to smoke
• For every death, 20 additional individuals will suffer at least 1 serious smoking related illness
Smoking Cessation

• 40% of smokers quit for at least one day
• 80% of smokers who attempt to quit continue smoking within one month
• Only 3% of smokers quit successfully each year
• 2/3 of smokers do not use any evidence-based treatment during quit attempt

Benefits of Cessation

21st-Century Hazards of Smoking and Benefits of Cessation in the United States
Prabhat Jha, M.D., Chinthane Ramassundarehettige, M.Sc., Victoria Landman, Ph.D., Brian Rusten, Ph.D., Michael Thun, M.D., Robert N. Anderson, Ph.D., Tim McAfee, M.D., and Richard Peto, F.R.S.

Benefits of Cessation

• 216, 917 adults between 1997 and 2004
• Data from the U.S. National Health Interview Survey (NHIS)
• Age-specific death rates among current smokers and non-smokers
• Affect of cessation after adjusting for educational level, alcohol consumption, and adiposity
  – This adjustment had no effect on age stratified hazard ratios.
Benefits of Cessation

- Overall mortality 3 times as high in smokers
- Smokers lose on average 10 years of life
Cessation Facts

- 20% of smokers are ready to quit at any given time
- 95% of unaided attempts end in failure
- Patients receive only 50% of recommended doses of medication
- Patients often complete less than half of scheduled counseling sessions
- 70% of smokers in the U.S. see a primary care physician each year

The Unwilling Patient

- Motivational Interviewing
  - Increased cessation by 30% in one study
- The “five R’s”
  - Relevant reasons to quit
  - Risks associated with continued smoking
  - Rewards for quitting
  - Roadblocks to successful quitting
  - Repetition of counseling at subsequent visits

The Unwilling Patient

- Nicotine Replacement
  - Meta-analysis 2767 smokers unwilling to quit
  - Randomly being assigned to nicotine-replacement therapy at 6 months
    - Asked to “reduce smoking”
    - 9% vs 5% quit at 6 months
  - Several studies showed 1/5 of smokers who did not quit reduced their smoking by 50% or more with such treatments
The Willing Patient

- Counseling
  - Consistent relationship between intensive counseling and abstinence
  - Meta-analysis of 35 randomized trials looking at 6 month abstinence
    - 14%: 1-3 minutes
    - 19%: 4-30 minutes
    - 27%: 31-90 minutes
  - 11%: no counseling
- USPSTF: Even “minimal counseling, lasting less than 3 minutes, has been shown to increase overall tobacco abstinence rates”
- 1-800-QUIT-NOW

Nicotine binds to and causes conformational changes in the nicotinic acetylcholine receptors in the brain

Consistent relationship between intensive counseling and abstinence

Pharmacotherapy

- Varenicline
- Cytisine
- Bupropion
- Nicotine replacement therapy
  - Patch
  - Lozenges
  - Gum
- E-cigarettes

Nicotinic Receptors

- Nicotine binds to and causes conformational changes in the nicotinic acetylcholine receptors in the brain
- Pentameric receptors
  - Two alpha 4, three beta 2 subunits
Varenicline

- Varenicline
  - developed by modifying the structure of the naturally occurring plant alkaloid cytisine
  - Competitively blocks the receptor
  - Partial agonist
    - Leads to partial stimulation and dopamine release
  - Suppresses symptoms of withdrawal and reduces reward

Varenicline Data

- Varenicline superior to placebo
- Varenicline more effective than sustained-release bupropion
  - At the end of 12 weeks of therapy, greater abstinence in varenicline group than bupropion or placebo
  - The 12 week 7 day point prevalence rate of abstinence
    - 50% Varenicline
    - 36% Bupropion
    - 21% placebo
  - At one year (9 months after drug discontinuation)
    - 29% varenicline vs 23% bupropion

Varenicline Data

- Duration of Therapy
  - Maintenance of abstinence after 12 weeks of initial treatment
  - An additional 12 weeks of varenicline superior to placebo at one year
  - Treatment for up to 6 months better at maintaining abstinence
- Two open label trials favor varenicline over nicotine replacement therapy at 4 weeks
  - 55.9% varenicline vs 43.2% nicotine patch
Varenicline Clinical Use

- Approved as a first line therapy
- Patients should be motivated
- Contraindicated for use in pregnancy and during lactation
- Quit date should be set for one week after initiation of therapy
- Target dose achieved in one week of 1mg twice daily
- Take with food to reduce nausea
- For problematic nausea, 1mg daily
- Renal impairment (CrCl < 30 ml per min): 0.5mg Daily

Varenicline Adverse Effects

- Nausea: Most common adverse effect
  - 30-50%
  - Taken with food helps
- Insomnia
- Abnormal dreams
- GI side effects
- Neuropsychiatric adverse events have been described
  - Changes in behavior should lead to discontinuation

Varenicline and Gradual Cessation

- JAMA 2015, February; 313
- 1,510 smokers would not quit abruptly but were willing to reduce smoking
- They were required to make a quit attempt within the next 3 months
- Asked to reduce smoking by 50% by week 4, 75% by week 8, quit altogether by week 12
- Primary end point was continuous abstinence rate during weeks 15-24
  - Abstinence rate wk 15-24: Varenicline 32.1% vs 6.9% in placebo
  - 1 year follow up: Varenicline 27% vs placebo 9.9%
Cystinine

- Cystinine: a plant-based alkaloid
  - Found in members of the Leguminosae family
  - Partial agonist of the nicotinic acetylcholine receptor
  - Half-life 4.8 hours
  - Low cost
    - Cystinine: $20-30 for 25 days
    - Nicotine-replacement therapy: $112-685 for 8-10 weeks
    - Varenicline: $474-501 for 12 weeks
    - Tobacco use at 1 ppd: $585-600 over 12 weeks

Cystinine

- Golden Rain Tree

Cystinine vs NRT

- NEJM 2014: December 18: Cystinine versus nicotine replacement was studied in a non-inferiority trial
  - 1310 adult smokers who were motivated were randomly assigned to cystinine for 25 days or NRT for 8 weeks
  - Smokers were recruited through the New Zealand national quit line
  - All participants offered low-intensity telephone behavioral counseling
    - Average of 3 calls 10-15 mins over an 8 week period
Cystinine vs NRT

- Participants asked to quit by 5th day
- Dosing:
  - Days 1-3: one tab every 2 hours while awake
  - Days 4-12: one tab every 2.5 hours
  - Days 13-16: one tab every 3 hours
  - Days 17-20: one tab every 4-5 hours (3 tablets per day)
  - Days 21-25: one tablet every 6 hours (2 tablets per day)
- Primary outcome: Abstinence at one month from quit day

Adverse events:
- More frequently in cystinine group
  - 31% vs 20%
- Nausea and vomiting
  - 30% vs 2%
- Sleep disorders
  - 28% vs 2%
- Median time to relapse longer in cystinine group:
  - 53 days vs 11 days

<table>
<thead>
<tr>
<th>Cystinine vs NRT</th>
<th>Day</th>
<th>Cystinine</th>
<th>NRT</th>
<th>Median time to relapse (days)</th>
<th>P Value</th>
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<td>196 (5)</td>
<td>1.5 (2.2 to 1.0)</td>
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Cystinine vs NRT

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Bupropion

- The first licensed non-nicotinic pharmacological therapy for smoking cessation
- First approved as an atypical antidepressant
- Blocks norepinephrine and dopamine re-uptake in the mesolimbic system and the nucleus accumbens
- Also an antagonist of nicotinic receptors

Bupropion

- Recommended dosage: 150mg twice daily
- Smokers should aim to 1 week after the start of treatment
  - Steady state in 5-8 days
- Shown to decrease nicotine/tobacco withdrawal symptoms
- Reduces post-cessation weight gain
- One meta-analysis has shown a significant increase in efficacy when combined with NRT
  - That effect not clearly seen across in the Cochrane review

Bupropion

- Adverse effects
  - Most common: Insomnia, dry mouth
  - Seizures, hypersensitivity reaction
- Contraindicated in patients taking MAO inhibitors, seizure disorders, abrupt withdrawal of alcohol or benzodiazepines
- Safe with cardiovascular disease
- Meta-analysis showed no increase in suicidality
Nicotine Replacement Therapy

- Most studied
- 6 month quit rates 20-30% consistent throughout the literature
- The bioavailability of nicotine by NRTs much less than cigarette smoke
- Safety profile is the best among first-line therapies
- Patch, gum, lozenge, inhaler, nasal spray

Nicotine Replacement Therapy

- The bioavailability of nicotine by NRTs much less than cigarette smoke
- Safety profile is the best among first-line therapies
- Transdermal patch offers continuous release over 16-24 hrs
- Oral formulations are short-acting, can be self-titrated
  - Control cravings

Nicotine Replacement

- Pre-Quit NRT
  - Modest benefit
  - Two studies used placebo-controlled design
    - Nicotine patch leading up to quit attempt vs placebo
    - One study revealed increase in 6 month abstinence
      - 22% vs 12%
    - Second study showed no significant difference
Nictotine Replacement Therapy

- Extended Treatment
  - Many smokers report cravings long after quitting
  - Relapse in distant weeks is common
  - Most treatment periods recommend 12 weeks
  - Wean over 12 week treatment period
  - 24 week vs 8 week treatment
    - Abstinence rates higher at 6 months in extended treatment
    - 32% vs 20%
    - 1 year favored extended treatment
  - Second trial looked at 26 vs 12 weeks
    - No difference
- Weak evidence that extended treatment is more efficacious

Nicotine Replacement

- Combination NRT
  - Randomized trials favor combination (patch + lozenge) vs all monotherapies
    - One trial at 6 months
      - 40% patch + lozenge vs 34% patch vs 34% lozenge
      - Clear benefit in reducing cravings
    - Patch + spray
      - 27% combined vs 21% patch vs 14% spray
      - Attenuated at 6 months
    - Arch Gen Psychiatry 2009
      - Five smoking cessation therapies
        - Nicotine patch vs lozenge highest efficacy: greatest latency to relapse relative to monotherapy
    - Studies generally support a modest increase in efficacy of combination NRT as opposed to any single formulation
      - At least short-term

E-cigarettes

- Deliver nicotine-containing aerosol (Vapor) by heating a solution made up of propylene glycol +/- glycol (glycerin)
- Marketed as a healthier alternative to tobacco smoking or useful for quitting smoking
- Engineering differences result in variability in how e-cigarettes convert nicotine solution to aerosol
  - Levels of nicotine and toxicants vary

Supri Health South Florida
E-cigarettes

• Review of 59 single brand e-cigarette web sites looked at the most popular claims
  – Healthier (95%)
  – Cheaper (93%)
  – Cleaner (95%)
  – Can be smoked anywhere (88%)
  – Do not produce second hand smoke (76%)
  – Cessation-related claims (64%)

• 10% of U.S. high school students in 2012 tried e-cigarettes based on population-based studies

Health Effects of E-cigarettes

• Propylene glycol
  – Eye irritation
  – Respiratory irritation
  – When heated and vaporized can form propylene oxide
    • Class B carcinogen

• Glycerol
  – Forms acrolein
    • Causes upper respiratory tract irritation
Levels of Toxicants in E-cigarettes

<table>
<thead>
<tr>
<th>Toxicant</th>
<th>Range in Cigarette</th>
<th>Range in E-Cigarette</th>
<th>Range in Conventional Cigarette</th>
<th>Content in Electronic Cigarette</th>
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Prepared using data from Germaine et al. *"E-cigarette induces oxidative stress, and NE, not determined.*

E-Cigarettes

- Tin, Nickel, Copper, Lead, Chromium found in samples of e-cigarettes
- Tin found to be cytotoxic to pulmonary fibroblasts
- Nickel
  - 2-100 times higher concentration than tobacco cigarette
  - Possibly come from heating element
- Metal nanoparticles can deposit in alveolar sacs, potentially causing local toxicity or enter the bloodstream

Health Effects of E-Cigarettes

- Vardavas et al revealed no effect on spirometry but increased dynamic airway resistance (18%)
  - Not seen in sham e-cigarettes
  - Small sample size
  - Concern that e-cigarettes can constrict peripheral airways
- Flouris et al found decreased FEV1/FVC in smokers but not in e-cigarette users
- Schober et al found elevated levels of exhaled nitric oxide in people using a nicotine e-cigarette, but not a nicotine-free e-cigarette
  - Attributed to inflammation
Health Effects of E-cigarettes

- Long-term biological effects of e-cigarettes are unknown
- No long term data

E-Cigarettes Cessation Data

- Polosa et al tested 23 subjects over 2 years
  - 18 subjects continued to smoke
    - 11 had reduced cigarette consumption by > 50%
    - Average reduction from 24 to 4 cigarettes
      - Statistically significant
    - 5 subjects quit
    - No control group

- Bullen et al
  - Randomized, controlled trial
  - 3 arms: nicotine patch, nicotine e-cigarettes, non-nicotine e-cigarettes
  - 57% nicotine e-cigarettes reduced consumption by > 50% vs 45% in non-nicotine e-cigarettes vs 41% in patch group
  - No statistically significant differences in abstinence at 6 months
- Not associated with successful quitting
E-Cigarettes

- What do I tell my patients:
  - The safest, most proven therapies are NRT, varenicline, and bupropion
  - Reasonable to support patients quit attempt if using e-cigarettes
  - E-cigarettes likely less toxic than tobacco smoke
  - Products are unregulated
  - Not proven to be used as cessation devices
  - Do not smoke indoors or around children or pregnant women
  - Set a quit date for e-cigarette use
    - Indefinite should be discouraged

Billing For Smoking Cessation

- 99406: 3-10 minute counseling
  - $40.00
  - Reimbursement: $16.17
- 99407: > 10 minutes of counseling
  - $75.00
  - Reimbursement: $31.04

Resources

- Tobaccofreeflorida.com
- 1-877-U-CAN-NOW
  - 1-877-822-6669
- Smoking cessation counseling
  - South Miami Hospital
  - Baptist Hospital
  - West Kendall Baptist Hospital
  - Broward
  - Mariners Baptist Hospital
- Run by the Florida Area Health Education Centers (AHEC.)
Summary

- Smoking cessation using evidence-based approaches do help smokers quit.
- Treatment is effective across a broad range of populations.
- Pharmacotherapies such as Varenicline, Bupropion, and NRT are first-line in the treatment of tobacco addiction.
- Counseling improves cessation success rates regardless of choice of pharmacotherapy.
- No long-term data regarding e-cigarettes – indefinite use is not recommended.
- Resources are available – many of which are free for the patient.
- Maintenance of cessation and avoidance of relapse will remain an ongoing struggle.