Smoking Cessation and Efficacy of New Treatments

Allan Prochazka, M.D., M.Sc.
Professor of Medicine
University of Colorado Denver
Objectives

- To apply current cessation guidelines in primary care settings
- To select the appropriate class of drug for patients wishing to quit smoking
- To understand the relative benefits and risks of the newer therapies
AHQR Guidelines

- Initially released 6/00, updated 4/08
- Based on review of > 3,000 studies
- Nearly all are RCT’s
- Probably the most evidence-based guideline in medicine
- Resulted in the 5A’s approach
  - Treating Tobacco Use and Dependence: 2008 Update, USDHHS, Public Health Service
Ask all patients 18 and older at each visit whether they smoke. Grade A recommendation USPSTF


Why every visit?

- Relapse among ex-smokers occurs even years after quitting
- Makes smoking salient for patients and providers
- Can add as an additional vital sign at check-in
- Triggers quit attempts by patients and advice/interventions by providers
- Electronic medical records can make this easier
Advise

- Strongest data are for physician advice
  - Other clinicians also likely to be effective
- Ideal to have a consistent approach across providers to reinforce the message
  - Patients will receive advice from multiple sources
- Best to avoid preaching/nagging, stay friendly and positive about the possibilities for change

Baxter S, et al. Nicotine Tob Res 2010;(epub 5/14/10)
Clear, Strong, Personalized

- **Clear**: ‘I think it’s important for you to quit smoking now and I can help you.’

- **Strong**: ‘As your doctor, I need you to know that quitting smoking is the best thing you can do for your health. The clinic staff and I will help you.’

- **Personalized**: ‘Smoking robs your body of oxygen and makes your claudication worse, quitting will greatly improve how far you can walk.’
‘I don’t want to quit, I’ve given up drugs, alcohol, sex. Smoking is my only pleasure in life’

- Don’t try to force cessation on the patient
- Continue to ask about smoking at each visit
- Many times these patients will surprise you and either quit on their own or be ready to quit at a future visit
Assess

- Identify willingness to quit
- ‘Are you willing to give quitting a try?’
- If yes, when do you want to quit?
  - If ready now, then provide assistance on quitting at this visit and deal with other problems at the next visit
  - If not ready, then work on motivation and on barriers
I want to quit, but…

- Identify the barriers
  - Fear of weight gain
  - Worry about urges
  - Too much stress, etc.

- Give tailored information about benefits of quitting, risks of smoking, availability of treatment
  - E.g. ‘We can use medication to take the edge off urges during the weeks after quitting’.
Assess

- Identify Tobacco Dependence
  - DSM IV R criteria
    - Withdrawal with cessation
    - Smoking in the face of medical illness
  - Fagerstrom
    - How soon after awakening do you smoke your first cigarette?
    - If < 5 minutes, then highly dependent
Assist

- Behavioral
- Drug Therapy
- Smokers wanting to quit need both
- Dose of each one can be tailored to the patient’s needs
Behavioral Interventions

- Key element is time with patient and empathic counselor
- More time, more benefit
- e.g. NRT or bupropion plus 2 phone calls 23% cessation at 24 months

Practical Actions

- Set a quit date within 2 weeks
- Tell family, friends, coworkers
- Make the home smoke free, start acting like a non-smoker
- Identify barriers to cessation
- Remove tobacco products from environment
Simple Behavioral Interventions

- Review prior quit attempts, learn from them
- Anticipate triggers and challenges
- Encourage others in the home to quit
- Provide a supportive clinical environment (e.g. ‘We can help you if you are having problems’)
- Provide options
  - Referral—not always available
  - Quitlines are proven to increase success rates, available in most states
- Self-help materials
Drug Therapy

- Valuable adjunct for anyone trying to quit, not just those who meet criteria for dependence

- Three Primary Classes of Agents
  - Nicotine Replacement Therapy (NRT)
  - Antidepressants
  - Nicotine Receptor Partial Agonists
Nicotine Replacement Therapy

- Gum
- Patch
- Lozenge
- Inhaler
- Nasal Nicotine

Other Potential Nicotine Related Approaches
- SNUS/Zonnic
- Electronic Cigarette
- Nicotine Vaccine
NRT

- Overall success rate comparable among the products
  - Odds ratios for quitting: Patch 1.66; Gum 1.43; Lozenge 2.00; Inhaler 1.90; Nasal Spray 2.02
- Doubles the quit rate
  - (e.g. 5-8% to 10-15%) compared to advice
  - (e.g. 10% to 17%) compared to placebo, overall odds ratio 1.58 (based on 40,000 patients studied, 132 trials)
    - L Stead et al. NRT for Smoking Cessation, Cochrane Review, 2008
- Selection based on side effects, patient preference, insurance coverage
- PDR duration of therapy 8-12 weeks
- Selected patients need longer therapy or higher doses
Nicotine Gum

- 2 forms (2 mg and 4 mg), 4 mg best for most smokers
- Available OTC and in generic forms and in various flavors
- Absorption is buccal, so park and chew
- Regular dosing better than ad lib
- Typical patient will use 5-8 pieces per day
- Retail cost $35-50 for 108 pieces
- **Side Effects**
  - Dental trauma, jaw pain, nausea, upset stomach

- **Duration of Use**
  - 8-12 weeks
  - 2-5% have trouble quitting gum
  - Long term use combined with behavioral therapy (up to 5 years) safe and effective, 25% validated quit rate in Lung Health Study
Transdermal Nicotine

- 3 strengths (21, 14, 7 mg/24hr)
- Some patients require higher doses (e.g. very heavy smokers), but for typical pack a day smoker 21mg is the starting dose
- 4-6 weeks on 21 mg, 2-4 weeks on 14 mg, then 2-4 weeks on 7 mg
- Costs $35-50 per 14 day supply
Side Effects

- Skin irritation (30%)
- Skin allergy (1-4%)
- Poor sleep/nightmares (10%)
- Arm pain (2-4%)
Nicotine Lozenge

- Approved 11/02
- Available OTC, 2 mg and 4 mg
- Allow lozenge to slowly dissolve, no chewing or swallowing of the lozenge—need to be careful not to develop too much saliva
- 20-30 minutes per lozenge
- Dose 20 max per day
- Side effects: hiccups, nausea, stomach upset, palpitations
- Cost $30-40.00 for box of 72 lozenges
Nasal Nicotine Spray

- Very rapid absorption of nicotine
- Dosing 0.5 mg per spray, one spray in each nostril is one dose (about the amount of nicotine in one cigarette)
- Typical patient uses 3-6 doses per day
- Side Effects: mostly irritation, face pain, perhaps more likely to result in difficulty stopping use due to fast absorption
- Costs $46.99 per 10 ml vial (100 doses)
Nicotine Inhaler

- Each cartridge 10 mg nicotine, 4 mg released, 2 mg absorbed
- Best with continuous puffing (80 deep inhalations over 20 minutes give 2 mg nicotine, about the same as one cigarette)
- Dosage 6-16 cartridges per day
- Side Effects: mouth/nose irritation
- Costs up to $160 per 168 cartridges (about 2-4 weeks’ supply)
High Dose NRT

- Not FDA approved, but has been tested in many trials
- Higher dose patches—not better when given as a routine for all smokers, best to titrate by intake/level of dependence
  - Useful for the very heavy smoker
  - Safety in trials and practice has been good
- Nicotine patch+nicotine gum or lozenge
  - Higher quit rate than either alone
  - Allows for steady level with ad lib gum
- Cochrane review (6 trials of high dose or combo therapy) odds ratio for quitting 1.21 (95% CI 1.03-1.42) compared to monotherapy
- Primary care trial found that cessation rate with patch/lozenge was 27% at 6 months compared to 18% with patch alone
- Main limitation is the cost of the therapy
Other Forms of Nicotine Delivery

- **SNUS**
  - Swedish fine ground tobacco, used orally, high nicotine, low amount of nitrosamines
  - Rapid buccal absorption of nicotine
  - Quite low smoking rates in Sweden, ? Related to use of SNUS
  - Unclear if oral cancer risk is really lower with this form of tobacco
  - Several brands available in US, Tobacco companies are pushing to market as a less hazardous alternative to smoking

- **Zonnic**
  - A sachet of peppermint flavored nicotine bound to crystalline cellulose bead
  - Quick absorption (30 minutes for level of 7.8 ng/ml)
  - Available in Sweden, not in US
  - Preliminary data indicate that smokers prefer either snus or zonnic to nicotine gum for cessation and that these two do reduce withdrawal symptoms; No long term quitting data
Electronic Cigarette

- Invented in China
- Lots of advertising on TV and internet, lots of word of mouth among smokers
- Battery powered, volatilizes nicotine, has flavorings to simulate smoking, gives off a water vapor smoke
- Package claims it contains a low thickness nicotine liquid and ‘does not contain hazardous substances’
- FDA analyses show it contains propylene glycol, felt to be generally safe, but also diethylene glycol with 1% content in one cartridge
  - Diethylene glycol has been a cause of several mass poisonings
  - Also found N-nitrosamines and other polycyclic aromatic hydrocarbons
    - Flouris AD, Oikonomou DN, BMJ 2010;340:215
- Not FDA approved, FDA would like to ban, but recent court ruling last month has blocked FDA actions to stop imports
- No safety testing, no data on efficacy for quitting
- Not something that we should be encouraging for our patients
Nicotine Vaccine

- Antibodies would bind to nicotine, prevent/slow penetration to brain, thus limiting reward potential
- Will likely require booster shots since levels of immunity decline
- At least two vaccines being developed
- Preliminary data suggest is well tolerated, if high antibody levels attained, then some evidence for increased cessation rates

Cornuz J, et al. PLOS One 2008;e2547
Antidepressants

- Bupropion (Zyban)—FDA approved in 1998
- Antidepressant, works in normal, non-depressed smokers
  - Relatively slow onset of action (7-10 days)
  - Dosage: 150 mg a day for 3 days, then 150 mg bid, but not much difference in effectiveness between 150 and 300 mg /day
  - Duration: 3 months, but longer term therapy is safe and effective
$70/month for generic long acting bupropion

Side Effects

- Common
  - Shaky, tremor
  - Headache
  - Dry mouth

- Rare but serious
  - Seizures
  - Avoid in those with epilepsy, active drug use, concomitant psychiatric medications, bulimia, MAOI use
Bupropion Efficacy

- Overall odds ratio for cessation 1.94 (95% CI 1.72 to 2.19) based on 19 trials
  - Hughes JR et al, Cochrane Review 2007

- Combination Therapy (patch + oral inhaler + bupropion) can work well with quit rates at 26 weeks 35% compared to 19% with patch alone and acceptable side effects

- Combined with lozenge, 30% 6 month quit rate

- Less weight gain than with patch
Bupropion Summary

- Very useful
  - Healthy populations (e.g. worksite)
  - Active cardiac disease

- Harder to use
  - Psychiatric comorbidity
  - Substance Abuse

- Has been tested in many populations including patients with COPD, African Americans; effect appears to be robust

- Bottom Line: very useful agent, main issue is caution with regard to seizure risk
Varenicline

- First designer drug for tobacco dependence
- Approved by FDA for smoking cessation in 2006
- Trade name (Chantix)
- A derivative of cytisine, derived from the golden rain tree
- Hasn’t really been a clinical reason to know about central nicotine receptors before this, but interactions with the α4β2 receptor are the main mechanism of action
- Acts as a partial agonist causing dopamine release, also is an antagonist and blocks the binding of exogenous nicotine

Varenicline Pharmacology

- Absorption high after oral dosing
- Half life 17 hours
- Low protein binding
- Excreted unchanged in the urine
- No digoxin/warfarin interactions seen
- Older patients with normal renal function have similar PK to younger smokers
Varenicline Clinical Trials

- So far about a dozen RCT’s
- Dose Ranging/Approval Trials
  - Smokers > 10 cigs/day, 18-65 yo
  - Excluded Psych, CVD, recent cessation rx, drug/etoh use
  - Drug started a week prior to quit day
  - Dose titrated up in 3-4 day increments
Dose Ranging Comparison to Bupropion

- 5 groups (n=638)
  - 0.3 mg qd; 1.0 mg qd; 1.0 mg bid varenicline
  - 150 mg SA bupropion
  - Placebo
  - Study drug started 1 week before quit day

- Subjects healthy, no contraindications to varenicline or bupropion, no psych hx, no etoh/drugs
Continuous Cessation Wks 4-52

- 0.3 mg qd  7.9%
- 1.0 mg qd  5.6%
- 1.0 mg bid  14.4%
- Bupropion SA 150 bid  6.3%
- Placebo  4.9%

Weight gain

- Greater among ‘cessators’
- +4 kg in placebo, 2.5 on varenicline, 1.7 on bupropion

Key Phase III Trial

- Gonzales et al

- 3 groups treated for 12 weeks
  - Varenicline titrated to 1.0 mg bid
  - Bupropion SA 150 mg bid (titrated)
  - Placebo

- Subjects
  - 18-75 yo, > 10 cigs/day, contraindications to bupropion, medically ill, psych dx’s, etoh/drugs, hepatic/renal impairment
Continuous Abstinence Rates

- Varenicline (n=352)
- Bupropion SR (n=329)
- Placebo (n=344)

### Treatment-Emergent Adverse Events (Including Those Not Necessarily Related to Study Drug)*

| No. (%) | Varenicline 
| (n = 349) | Bupropion SR 
| (n = 329) | Placebo 
| (n = 344) |
|---|---|---|
| Any adverse event | 275 (78.6) | 258 (78.4) | 257 (74.7) |

#### Most Frequent Adverse Events*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Varenicline</th>
<th>Bupropion SR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>98 (28.1)</td>
<td>41 (12.5)</td>
<td>29 (8.4)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>23 (6.6)</td>
<td>29 (8.8)</td>
<td>19 (5.5)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>20 (5.7)</td>
<td>14 (4.3)</td>
<td>10 (2.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>19 (5.4)</td>
<td>23 (7.0)</td>
<td>13 (3.8)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>49 (14.0)</td>
<td>72 (21.9)</td>
<td>44 (12.8)</td>
</tr>
<tr>
<td>Abnormal dreams†</td>
<td>36 (10.3)</td>
<td>18 (5.5)</td>
<td>19 (5.5)</td>
</tr>
<tr>
<td>Irritability</td>
<td>21 (6.0)</td>
<td>17 (5.2)</td>
<td>20 (5.8)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>20 (5.7)</td>
<td>13 (4.0)</td>
<td>13 (3.8)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>54 (15.5)</td>
<td>47 (14.3)</td>
<td>42 (12.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (6.0)</td>
<td>19 (5.8)</td>
<td>20 (5.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>20 (5.7)</td>
<td>17 (5.2)</td>
<td>18 (5.2)</td>
</tr>
</tbody>
</table>

#### Study Drug Treatment Discontinuations Due to Adverse Events‡

<table>
<thead>
<tr>
<th>Category</th>
<th>Varenicline</th>
<th>Bupropion SR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>30 (8.6)</td>
<td>50 (15.2)</td>
<td>31 (9.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (2.6)</td>
<td>6 (1.8)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

*Abbreviation: bupropion SR, sustained-release bupropion.

†Treatment-emergent adverse events were defined as adverse events that began or increased in severity during study-drug treatment or up to 7 days after the last dose. Reported events occurred at 5% or more for varenicline and at a higher frequency than reported for placebo.

‡Self-described as any change in dreaming, such as vivid dreams or increased frequency of dreaming.

†Includes participants who discontinued study drug treatment but remained in the study, as well as those who discontinued the overall study.

Conclusions from Approval Trials

- Varenicline effective compared to placebo with at least a doubling of the quit rate OR 2.33 (95% CI 1.95-2.88)
  - Cahill C. Cochrane Review, 2008
- Moderately (OR 1.52, 95% CI 1.22-1.88) better quit rate than bupropion SA
- Perhaps better than NRT (OR 1.33 (1.01-1.71), but few trials
- Nausea was the most predominant side effect
- Rate of drug discontinuation was relatively low
Considerations with Varenicline

- Studies included basically healthy and young subjects
- Drug is renally excreted, so if EFGR is < 50 ml/min be cautious since drug exposure is increased
- Drug is removed by dialysis, but levels are 2.7 time higher than in normals
- Nausea can be persistent in some patients, dose titration limits this effect
- As with NRT abnormal dreams are relatively common
Psychiatric Morbidity with Varenicline

- In approval RCT’s 2 cases of psychosis
- Numerous case reports since approval
  - Worsening of schizophrenia 5 days after starting varenicline in patient who was stable on low dose neuroleptic
  - Mania requiring hospitalization 1 week after starting varenicline in a bipolar patient who was stable on valproate
    - Am J Psych 2007;164:1269-1270
- UK 2682 pts in general practice
  - 2 cases of attempted suicide
  - Mood change/depression 1.7%
  - Anxiety 1.2%
- VA PBM July 2009, 149 cases of suicidal behaviors out of approximately 100,000 patients treated
  - VA Bulletin, July 2, 2009
## UK Surveillance

<table>
<thead>
<tr>
<th></th>
<th>Varenicline</th>
<th>Bupropion#</th>
<th>Nicotine</th>
<th>Control*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Market Share</td>
<td>13%</td>
<td>7%</td>
<td>77%</td>
<td>n/a</td>
</tr>
<tr>
<td>Suicides</td>
<td>22</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Attempts</td>
<td>46</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ideation</td>
<td>377</td>
<td>104</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Agression</td>
<td>172</td>
<td>131</td>
<td>8</td>
<td>22</td>
</tr>
</tbody>
</table>


* Amoxicillin

# all indications
FDA Black Box on Bupropion and Varenicline

- July 2009
  - Watch for changes in behavior, hostility, agitation, depressed mood, suicidal thinking and behavior
  - Stop the meds if above occur and monitor until resolved
  - Rates of suicide and depression are low (less than 1/1000), but warrants caution with both drugs in patients with psychiatric disorders and also means that both should be prescribed only with adequate followup
Other Varenicline Studies

- VA Observational Trial
  - 30% overall cessation rate
  - Less likely to succeed if had concomitant mental illness
    Purvis TL, Ann Pharmacother 2009;43:862-867

- Varenicline combined with bupropion
  - Small open-label Phase II trial (n=38)
  - 58% cessation rate at 6 months
  - May be an option in the future

- Varenicline in CVD pts
  - RCT, n=714, stable CVD
  - Quit rate at one year was 19% compared to 7% with placebo
Varenicline’s Place in Therapy

- Expensive ($370 for 168 1 mg tabs, enough for 12 weeks), price seems remarkably similar to that of 3 months of Marlboro’s
- Probably best to save for those who have failed first line therapies
- VA Guidelines
  - Second line agent
  - Avoid in patients with psychiatric disorders unless working collaboratively with mental health provider
  - Monitor after starting therapy on regular basis
Practical Use of Drug Therapy in Primary Care

- Nearly all patients will benefit from drug therapy in addition to brief advice
- For a generally healthy population of smokers, all three FDA approved methods are effective and safe (NRT, bupropion, varenicline)
- With psychiatric co-morbidity, be cautious with varenicline and bupropion
- Patient preference, prior quitting experience and costs will often determine which drug is the best
- Combination therapy (either high dose NRT or NRT+bupropion) usually works better, especially for more heavily dependent
- Use varenicline for failures of first line therapies
- Realistically, 10-15% long-term cessation is possible in PC settings
Future Directions

- More study needed to determine optimal drug combinations
- Most patients fail any given attempt, so recycling them and trying different agents/more intensive behavioral support
- The best approach to psychiatric patients and those with comorbid conditions remains to be determined
- Today have 3 major drug classes that are approved for cessation, so we have many more options than in the past