Nicotine replacement therapy for smoking cessation

- Updated 2010 Dec 06 05:28:00 PM: nicotine replacement therapy for patients interested in reducing tobacco consumption without quitting may increase smoking cessation rates (Cochrane Database Syst Rev 2010 Sep 8) view update
- nicotine patch and lozenger had similar quit rates overall but lozengers had higher quit rates for smoking associated with stress (Drug Alcohol Depend 2010 Mar 1) view update
- extended duration nicotine patch therapy may not improve long-term abstinence compared to standard duration therapy (Ann Intern Med 2010 Feb 2) view update

Related Summaries:

- Nicotine for prescribing information
- Tobacco use disorder
- Counseling for tobacco cessation
- Bupropion for smoking cessation
- Varenicline

Overview:

- nicotine replacement therapy (NRT) is effective for smoking cessation (level 1 [likely reliable] evidence)
    - effective forms of NRT include gum, transdermal patch, sublingual tablet/lozenge, oral inhaler and nasal spray
    - various types of nicotine replacement products appear equally efficacious for achieving short-term abstinence (level 2 [mid-level] evidence)
- nicotine replacement therapy for reduction in cigarette consumption may increase smoking cessation rates (level 2 [mid-level] evidence)
- nicotine patch therapy prior to quitting smoking may increase smoking abstinence rates (level 2 [mid-level] evidence)

- insufficient evidence to support nicotine replacement therapy in adolescents
- combination of NRT approaches
    - addition of nicotine nasal spray for 1 year to use of nicotine patch for 5 months improves abstinence rates (level 1 [likely reliable] evidence)
    - nicotine patch plus nicotine lozenge increases 6-month quit rate (level 1 [likely reliable] evidence)
    - addition of nicotine patch to nicotine inhaler may improve short-term quit rates (level 2 [mid-level] evidence)
- comparative efficacy with other medications
    - bupropion may be more effective than nicotine replacement (level 2 [mid-level] evidence)
    - varenicline may increase continuous abstinence rates more than transdermal nicotine (level 2 [mid-level] evidence)
- combination of bupropion plus nicotine replacement has inconsistent evidence
    - combination bupropion plus nicotine inhaler may be more effective than either monotherapy, bupropion appears more effective than nicotine inhaler (level 2 [mid-level] evidence)
    - addition of bupropion for 7 weeks appears no more effective than placebo in patients taking nicotine replacement therapy and counseling (level 2 [mid-level] evidence)
- safety
    - nicotine replacement therapy does not appear to acutely increase risk of myocardial infarction, stroke or death (level 2 [mid-level] evidence)
    - nicotine replacement therapy appears safe in patients with cardiac disease (level 2 [mid-level] evidence)
    - nicotine replacement therapy associated with increased mortality in critically ill patients (level 2 [mid-level] evidence)

United States Public Health Service (PHS)recommendations(1):

- combination of counseling and medication is more effective than either alone and both should be offered (PHS Strength of Evidence A)
- effective medication should be offered to most patients unless contraindicated (PHS Strength of Evidence A)
- populations in which there is insufficient evidence for effectiveness include
    - pregnant women
    - smokeless tobacco users

    - adolescents
    - light smokers (< 10 cigarettes/day)
- numerous types of nicotine replacement therapy are effective (PHS Strength of Evidence A)
    - nicotine gum (heavy smokers should be offered 4 mg rather than 2 mg gum [PHS Strength of Evidence B])
    - nicotine inhaler
    - nicotine lozenge is effective (PHS Strength of Evidence B)
    - nicotine nasal spray
    - nicotine patch
    - combination therapies
        - nicotine patch and bupropion SR
        - nicotine patch and nicotine inhaler
        - nicotine patch for 14 weeks and another nicotine replacement therapy (for example, gum or spray)
    - over the counter nicotine patch therapy is effective (PHS Strength of Evidence B)
- for smokers unwilling to quit, provide motivational interviewing (PHS Strength of Evidence B)

▼Efficacy of Nicotine Replacement Therapy

Overall efficacy:

- **nicotine replacement therapy (NRT) is effective for smoking cessation (level 1 [likely reliable] evidence)**
    - based on 4 meta-analyses
    - Cochrane review of 132 randomized trials evaluating NRT and assessing abstinence after at least 6 months
        - smoking cessation rates comparing NRT vs. control
            - 18% vs. 11.3% for nicotine gum ($p < 0.00001$, NNT 15) in analysis of 53 trials with 19,090 participants
            - 15.8% vs. 9.9% for nicotine patch ($p < 0.00001$, NNT 17) in analysis of 41 trials with 18,237 participants

        - 16.1% vs. 8.1% for nicotine sublingual tablet/lozenge ($p < 0.00001$, NNT 13) in analysis of 6 trials with 3,109 participants
        - 17.1% vs. 9.1% for inhaled nicotine ($p = 0.0002$, NNT 13) in analysis of 4 trials with 976 participants
        - 23.9% vs. 11.9% for nicotine nasal spray ($p < 0.00001$, NNT 9) in analysis of 4 trials with 887 participants
    - weak evidence that combinations of NRT are more effective
    - higher nicotine doses may be more effective in heavy smokers
    - 1 trial found bupropion more effective than nicotine patches
    - Reference – systematic review last updated 2007 Nov 1 (Cochrane Library 2008 Issue 1:CD000146)
    - Cochrane for Clinicians summary of earlier version can be found in Am Fam Physician 2001 Jun 1;63(11):2245 full-text (correction can be found in Am Fam Physician 2002 Feb 15;65(4):560, commentary can be found in Am Fam Physician 2001 Jun 1;63(11):2130)
- systematic review of 69 randomized placebo-controlled trials evaluating 7 pharmacotherapies for smoking cessation in 32,908 patients
    - smoking abstinence assessed by biochemically validated measures at 6 and 12 month follow-up
    - varenicline, nicotine nasal spray, bupropion, transdermal nicotine, nicotine tablets, and nicotine gum significantly better than placebo for smoking cessation ($p < 0.05$ for each)
    - non-significant trend favoring nicotine inhaler
    - Reference – CMAJ 2008 Jul 15;179(2):135 full-text, correction can be found in CMAJ 2008 Oct 7;179(8):802 full-text, editorial can be found in CMAJ 2008 Jul 15;179(2):123 full-text, commentary can be found in CMAJ 2008 Nov 4;179(10):1037 full-text
- systematic review of 1-year outcomes with limited methodological quality assessment
    - systematic review of 12 randomized placebo-controlled trials of nicotine replacement therapy and outcomes reported at 1 year with 4,792 patients

        - reviewers did not state methods of quality assessment or accounting for dropouts
        - success defined for each trial as most conservative estimate of success, such as continuous abstinence rates with biochemical confirmation
        - nicotine replacement therapy included nicotine patch (5 trials), nicotine gum (4 trials) and nicotine nasal spray (3 trials)
        - trial duration ranged from 2–8 years, weighted mean 4.3 years
        - comparing nicotine replacement therapy vs. placebo
            - 12.2% vs. 7% long-term smoking cessation ($p < 0.001$, NNT 20)
            - 18.2% vs. 10.1% smoking cessation at 1 year (NNT 13)
        - Reference – Tob Control 2006 Aug;15(4):280
    - meta-analysis of 21 randomized trials with subgroup analyses by gender
        - nicotine replacement therapy more effective for men than placebo at 3, 6, and 12 month follow-ups
        - nicotine replacement therapy more effective for women only at the 3 and 6 month follow-ups
        - Reference – J Consult Clin Psychol 2004 Aug;72(4):712 in ACP J Club 2005 Jan-Feb;142(1):13
- **nicotine replacement therapy for patients interested in reducing tobacco consumption without quitting may increase smoking cessation rates (level 2 [mid-level] evidence)**
    - based on Cochrane review of trials with methodologic limitations
    - systematic review of randomized trials evaluating interventions to reduce number of cigarettes smoked (16 trials) or products to reduce damage caused by tobacco (3 trials) in 9,760 patients
    - allocation concealment inadequately described in 16 trials; 3 trials with adequate allocation had high dropout rates
    - insufficient evidence to evaluate reduced-exposure tobacco products
    - nicotine replacement therapy compared with placebo in analysis of 9 trials with 3,429 patients
        - nicotine replacement therapy associated with
            - more patients achieving ≥ 50% reduction in cigarettes per day in analysis of 9 trials with 3,429 patients

            - risk ratio (RR) 1.72 (95% CI 1.41–2.1)
            - NNT 13–34 assuming 7.2% reduction in placebo group
        - increased smoking cessation at long-term follow-up in analysis of 9 trials with 3,429 patients
            - RR 1.73 (95% CI 1.36–2.19)
            - NNT 14–47 assuming 6% cessation in placebo group
    - bupropion not significantly effective for reduction or cessation in 1 trial
    - lifestyle consultation and motivational interviewing associated with reduced cigarette consumption compared to untreated controls in 1 trial, but very few people who were offered smoking reduction group attended
    - computerized scheduled reduction and reduction by selective elimination of cigarettes had similar results in 1 trial
    - repeated telephone counselling and mailings not associated with significant reduction at 1 year in 1 trial
    - Reference – Cochrane Database Syst Rev 2010 Sep 8;(9):CD005231
    - similar findings also reported in systematic review of 7 randomized trials (all included in Cochrane) of nicotine replacement therapy for 'cut down to quit' smoking (Health Technol Assess 2008 Feb;12(2):iii full-text), also published in BMJ 2009 Apr 2;338:b1024 full-text, commentary can be found in BMJ 2009 Apr 29;338:b1730 (commentary can be found in BMJ 2009 May 20;338:b1979)
- **either motivational interviewing, or combination of counseling to reduce smoking and nicotine replacement therapy (NRT), may improve quit rates in smokers uninterested in quitting (level 2 [mid-level] evidence)**
    - based on randomized trial without blinded outcome assessment
    - 616 smokers willing to participate in the study ($75 provided for participation) but not interested in participating in active smoking cessation study were randomized to 1 of 3 groups
        - no treatment
        - counseling to cut back on smoking and offer of NRT at 0 and 3 weeks with brief advice to quit at 6 weeks

        - motivational interviewing and offer of NRT at weeks 0 and 3 and brief advice to quit at 6 weeks
    - entire study was conducted by telephone, outcomes were self-reported and interviewers were not blinded to treatment assignment

Outcomes (p values vs. No treatment

	Smoking reduction counseling plus nicotine replacement therapy	Motivational interviewing	No treatment
Abstinence for prior 7 days at 24 weeks	18% (p < 0.001, NNT 8)	23% (p < 0.001, NNT 6)	4%
Abstinence for prior 7 days at 6 weeks	1%	1%	1%
Any quit attempt at 24 weeks	54% (p < 0.001, NNT 4)	59% (p < 0.001, NNT 3)	24%
Any 24-hour quit attempt at 24 weeks	43% (p < 0.001, NNT 4)	51% (p < 0.001, NNT 3)	16%

    - Reference – J Consult Clin Psychol 2004 Jun;72(3):371, commentary can be found in Evidence-Based Medicine 2005 Jan-Feb;10(1):18
- **insufficient evidence to support nicotine replacement therapy in adolescents**
    - based on Cochrane review with inadequate power in high quality trials
    - systematic review of 24 randomized or controlled trials of interventions for smoking cessation in > 5,000 regular tobacco smokers < 20 years old
    - 2 trials addressed nicotine replacement therapy
        - nicotine replacement associated with non-significant trend toward increased abstinence at 6 months in 1 underpowered trial with 120 adolescents
        - addition of bupropion to nicotine patch had no effect in 1 trial with 211 adolescents

- Reference – Cochrane Database Syst Rev 2010 Jan 20;(1):CD003289

Transdermal nicotine:

- **nicotine patch therapy prior to quitting smoking may increase smoking abstinence rates (level 2 [mid-level] evidence)**
  - based on systematic review with limited methodologic quality assessment
  - systematic review of 4 randomized trials meeting the following criteria
    - smokers interested in quitting (not just reduction)
    - all smokers treated with nicotine patches after quit date
    - smokers randomized to nicotine patch vs. control before quit date (pre-quit treatment)
    - biochemically verified continuous abstinence rates 4-6 weeks after target quit date reported
  - trials were heterogeneous
    - 2 trials included mecamylamine as adjunct following target quit day
    - 1 trial evaluated mecamylamine during pre-quit treatment
    - 2 trials varied type of cigarettes used during pre-quit treatment
    - pre-quit treatment period 2 weeks in 3 trials and 4 weeks in 1 trial
  - trial sample sizes were 379, 200, 96 and 80 (total 755 participants)
  - allocation concealment, follow-up rates and intention-to-treat analysis not evaluated or reported
  - 6-week abstinence rates
    - higher in all 4 trials with active treatment (23%, 29%, 50%, 40%) than control (13%, 19%, 23%, 36%)
    - 2 of 4 trials reported statistically significant differences
    - meta-analysis found statistically significant difference with pooled odds ratio 1.96 (95% CI 1.31-2.93)
  - 6-month abstinence rates
    - higher in all 4 trials with active treatment (22%, 22%, 21%, 30%) than control (11%, 12%, 13%, 15%)
    - 1 of 4 trials reported statistically significant differences
    - meta-analysis found statistically significant difference with pooled odds ratio 2.17 (95% CI 1.46-3.22)

    - Reference – Addiction 2008 Apr;103(4):557
- **nicotine patch therapy enhances 6-month quit rates as adjunct to brief primary care intervention**
    - based on randomized trial
    - 369 smokers of at least 20 cigarettes/day at 21 primary care sites in Nebraska randomized to nicotine vs. placebo patch therapy for 10 weeks in addition to 2 brief primary care visits for smoking intervention
    - comparing nicotine patch vs. placebo
        - 3-month abstinence rate 23.4% vs. 11.4%
        - 6-month abstinence rate 18.5% vs. 10.3%
        - 1-year abstinence rates of 14.7% vs. 8.7% not statistically significant
        - among smokers > 45 years old, 18.8% vs. 0 achieved 12-month abstinence
    - highest quit rates were achieved by participants who specifically contacted the site to enroll in the study or to obtain a prescription for nicotine patches
    - nicotine patches had higher 1-year abstinence rates (19.1% vs. 5%) among those with high nicotine dependency scores (Fagerstrom ≥ 7), no significant difference in patients with low Fagerstrom scores (< 7)
    - Reference – Arch Fam Med 1998 Sep-Oct;7(5):425 full-text
- **extended duration nicotine patch therapy may not improve long-term abstinence compared to standard duration therapy (level 2 [mid-level] evidence)**
    - based on randomized trial with high dropout rate
    - 568 adult smokers without comorbid conditions randomized to extended duration vs. standard duration therapy with nicotine patch (Nicoderm CQ)
        - extended duration therapy was nicotine patch 21 mg for 24 weeks
        - standard duration therapy was nicotine patch 21 mg for 8 weeks followed by placebo patch for 16 weeks
    - 20% of patients lost to follow-up at 24 weeks and 28% lost at 52 weeks, dropouts counted as treatment failures
    - comparing extended vs. standard therapy
        - point prevalence of carbon monoxide-confirmed abstinence

            - at 24 weeks 31.6% vs. 20.3% (p = 0.002, NNT 9)
            - at 52 weeks 14.5% vs. 14.3% (not significant)
        - continuous abstinence
            - over 24 weeks in 19.2% vs. 12.6% (p = 0.032, NNT 16)
            - over 52 weeks 0.7% vs. 1% (not significant)
    - no significant differences in time to relapse or adverse events
    - Reference – Ann Intern Med 2010 Feb 2;152(3):144
- **nonprescription nicotine patch appears to improve quit rates**
    - **nicotine patch used in nonprescription setting associated with quit rates comparable to those reported for medical settings (level 2 [mid-level] evidence)**
        - based on randomized trial with allocation concealment not stated
        - 802 adults who smoked at least 20 cigarettes/day for 1 year in 4 shopping mall precincts randomized to nicotine patch vs. placebo for 6 weeks with 18 weeks of follow-up
        - guidance consisted only of package instructions and smoking cessation self-help booklet
        - smoking cessation confirmed with carbon monoxide < 8 ppm in expired breath
        - 12% vs. 5.5% total abstinence from week 3 through week 6
        - 19.5% vs. 7.5% not smoking at 6 weeks
        - 8.2% vs. 4% nonsmokers at 24 weeks
        - 57% vs. 39% reported at least 1 adverse effect
        - Reference – Arch Fam Med 1998 Nov-Dec;7(6):569 full-text
        - *DynaMed commentary* -- 24 patients need to be treated for 1 more nonsmoker at 24 weeks
    - **nonprescription nicotine patch appears more effective than placebo patch (level 2 [mid-level] evidence)**
        - based on meta-analysis of 4 trials (only 2 were randomized)
        - Reference – Tob Control 2003 Mar;12(1):21, commentary can be found in Bandolier 2003 Apr;110:7
- **24-hour nicotine patch (Nicopatch) reported to be more effective in alleviating withdrawal-induced sleep disturbance based on single night sleep recordings than 16-hour nicotine patch (Nicorette) (level 3 [lacking direct] evidence)**

    - based on open-label randomized crossover trial without clinical outcomes
    - 20 heavy smokers randomized to 24-hour vs. 16-hour nicotine patch for single night sleep recordings (so not clear if results apply to longer-term use)
    - Reference – Sleep Med 2006 Mar;7(2):147
- **nicotine patch may not be effective during pregnancy (level 2 [mid-level] evidence)**
    - based on randomized trial with poor medication compliance
    - 250 pregnant smokers randomized to nicotine vs. placebo patches for 11 weeks
    - Reference – Obstet Gynecol 2000 Dec;96(6):967
- **cost effectiveness could be increased by prescribing 2-week course of patches with refills** instead of an entire month's supply, because most failures of smoking cessation occur in the first 2 weeks (JAMA 1996 Apr 24;275(16):1247), commentary can be found in JAMA 1996 Aug 7;276(5):371, J Fam Pract 1996 Aug;43(2):125, ACP J Club 1996 Sep-Oct;125(2):53
- **addition of nicotine patch therapy to cognitive behavioral group therapy may help adolescent smokers quit (level 2 [mid-level] evidence)**
    - based on randomized trial with high dropout rate
    - 120 adolescents aged 13-17 years who smoked 10 or more cigarettes per day, scored at least 5 on Fagerström Test of Nicotine Dependence, and were motivated to quit smoking were randomized to nicotine patch (Nicoderm 21 mg, or 14 mg if weight < 100 lbs [45 kg] and smoking < 20 cigarettes/day) vs. nicotine gum (Nicorette 4 mg, or 2 mg if smoking < 25 cigarettes/day) vs. placebo (patch and gum) for 12 weeks, all patients received cognitive behavioral group therapy
    - prolonged abstinence rates (continuous abstinence as of 2 weeks after randomization) confirmed with exhaled carbon monoxide ≤ 6 ppm
    - prolonged abstinence analyzed on intention-to-treat basis, but only 53 patients (44%) completed the study

Prolonged abstinence rates

	Nicotine patch	Nicotine gum	Placebo
Prolonged abstinence at 3	17.7%*	6.5%	2.5%

	Prolonged abstinence rates		
	Nicotine patch	**Nicotine gum**	**Placebo**
months			
Prolonged abstinence at 6 months	20.6%	8.7%	5%
* p < 0.05 vs. placebo			

- Reference – Pediatrics 2005 Apr;115(4):e407 full-text

Nicotine polacrilex gum:

- Thrive (nicotine polacrilex gum) available without a prescription; 2 mg if smoking < 25 cigarettes/day, 4 mg if ≥ 25 cigarettes/day (Monthly Prescribing Reference 2007 Aug:A-12)
- clinicians should offer 4 mg nicotine gum instead of 2 mg to highly dependent smokers (for example, smoking within 30 minutes after waking) (PHS Strength of Evidence B)[1]
- nicotine gum in pregnancy associated with increase in birth weight and gestational age, but not smoking cessation rates compared with placebo (level 2 [mid-level] evidence
- **nicotine gum plus decreased cigarette consumption 4 weeks prior to quit date not associated with increased abstinence (level 2 [mid-level] evidence)**
  - based on randomized trial without blinding
  - 314 adult smokers (≥ 15 cigarettes/day) randomized to precessation intervention vs. usual care
  - precessation intervention was nicotine gum plus reduction in cigarette consumption by half for 4 weeks prior to quit date
  - all participants had nicotine gum (≥ 10 pieces/day) for 8 weeks following quit date
  - comparing precessation nicotine gum vs. usual care
    - self-reported abstinence 8 weeks after quit date 41.6% vs. 44.4% (not significant)
    - biochemically verified abstinence at 12 months 20.8% vs. 19.4% (not significant)

- Reference – Arch Intern Med 2009 Jun 8;169(11):1028, editorial can be found in Arch Intern Med 2009 Jun 8;169(11):1022

Nicotine polacrilex lozenge:

- lozenge provides about 25% more nicotine than gum (Treat Guidel Med Lett 2008 Sep;6(73):61 TOC)
- **nicotine polacrilex lozenge may be effective for smoking cessation (level 2 [mid-level] evidence)**
  - based on randomized trial with allocation concealment not stated
  - 1,818 smokers were randomized to nicotine lozenges (2 mg or 4 mg based on nicotine dependence assessed by time to first cigarette of the day) vs. placebo lozenges for 1 year
  - nicotine lozenges significantly improved 28-day abstinence at 6 weeks in
    - low-dependence/2-mg group (46% vs. 29.7%, NNT 7)
    - high-dependence/4-mg group (48.7% vs. 20.8%, NNT 4)
  - significant effects maintained for 1 year
  - nicotine lozenges reduced craving and withdrawal
  - Reference – Arch Intern Med 2002 Jun 10;162(11);1267 full-text, commentary can be found in Arch Intern Med 2002 Dec 9-23;162(22):2632 (correction can be found in Arch Intern Med 2003 Mar 10;163(5):571)
- nicotine polacrilex (Commit Lozenge) FDA approved for nonprescription use; 2-count Commit Lozenge packs to be available in 2 mg and 4 mg (PDR Monthly Prescribing Guide 2002 Dec:1(12):17)
- Commit Lozenge
  - dosed as
    - 4 mg for patients who normally start smoking within 30 minutes of awakening
    - 2 mg if first cigarette > 30 minutes after awakening
  - selected dose lozenge sucked every
    - 1-2 hours for 6 weeks
    - then every 2-4 hours for 3 weeks
    - then every 4-8 hours for 3 weeks
  - chewing lozenges releases nicotine too fast and can cause gastrointestinal upset

    - acidic drinks reduce absorption
    - Reference – Prescriber's Letter 2002 Dec;9(12):69

Nicotine oral inhaler:

- Nicotrol Inhaler (Monthly Prescribing Reference 1997 Jun;A-21, Am Fam Physician 1997 Jul;56(1);283) for oral inhalation, acts like cigarette without tobacco; nicotine 4 mg dose in plastic cartridge containing 10 mg, each cartridge last 20 minutes with frequent continuous puffing equivalent to 2 cigarettes (Monthly Prescribing Reference 1998 Jul;A-25,235)
- **nicotine oral inhaler reduces smoking over 2 years (level 1 [likely reliable] evidence)**
    - 400 volunteers willing to reduce smoking but not quit were randomized to active vs. placebo inhaler as needed for up to 18 months
    - sustained reduction rates comparing active vs. placebo inhaler
        - 26% vs. 9% at 4 months ($p < 0.001$, NNT 7)
        - 9.5% vs. 3% at 2 years ($p = 0.012$, NNT 16)
    - Reference – BMJ 2000 Aug 5;321(7257):329, editorial can be found in BMJ 2000 Aug 5;321(7257):311

Nicotine nasal spray:

- long-term follow-up of trial of 227 heavy smokers randomized to nicotine spray vs. placebo
    - 33% vs. 14% abstinence at 1 year
    - 15% vs. 6% abstinence at 3.5 years
    - 10.8 patients need to be treated for 1 to have long-term cessation
    - Reference – BMJ 1998 Mar 14;316(7134):830

Other nicotine products:

- nicotine lollipops and lip balm currently considered illegal by FDA (FDA Talk Paper 2002 Apr 10)

▼Combination Nicotine Therapies

Nicotine patch plus nasal spray:

- **addition of nicotine nasal spray for 1 year to use of nicotine patch for 5 months improves abstinence rates (level 1 [likely reliable] evidence)**
    - based on randomized trial
    - 237 smokers aged 22–66 years randomized to nicotine patch for 5 months (15 mg for 3 months, 10 mg for 1 month, 5 mg for 1 month) plus placebo nasal spray for 1 year vs. nicotine patch for 5 months plus nicotine nasal spray for 1 year
    - sustained abstinence rates comparing nicotine nasal spray vs. placebo nasal spray
        - 51% vs. 35% at 6 weeks (p = 0.011, NNT 7)
        - 37% vs. 25% at 3 months (p = 0.045, NNT 9)
        - 31% vs. 16% at 6 months (p = 0.005, NNT 7)
        - 27% vs. 11% at 1 year (p = 0.001, NNT 7) with 0 vs. 4 persons still using nasal spray
        - 16% vs. 9% at 6 years (p = 0.077)
    - Reference – BMJ 1999 Jan 30;318(7179):285 full-text, correction can be found in BMJ 1999 Mar 20;318(7186):764, editorial can be found in BMJ 1999 Jan 30;318(7179):289 full-text, commentary can be found in ACP J Club 1999 Jul-Aug;131(1):12

Nicotine patch plus nicotine lozenge:

- **nicotine patch plus nicotine lozenge increases 6-month quit rate (level 1 [likely reliable] evidence)**
    - based on randomized trial
    - 1,504 smokers (≥ 10 cigarettes/day for at least 6 months) randomized to 1 of 6 groups (in addition to 6 individual counseling sessions)
        - bupropion 150 mg twice daily for 9 weeks total (1 week prequit and 8 weeks postquit)
        - nicotine lozenge 2 or 4 mg (based on dose-for-dependence level instructions) for 12 weeks postquit
        - nicotine patch (24-hour patch, 21, 14, and 7 mg, titrated down during 8 weeks postquit)
        - combination nicotine patch plus nicotine lozenge
        - combination bupropion plus nicotine lozenge
        - placebo (5 different conditions matched to active treatment conditions)

    - carbon monoxide–confirmed abstinence rates (among 1,424 patients for whom data was available)
        - at 8 weeks
            - 53.6% patch plus lozenge
            - 50.4% bupropion plus lozenge
            - 44.7% patch alone
            - 40.4% lozenge alone
            - 40.2% bupropion alone
            - 30.2% placebo
        - at 6 months
            - 40.1% patch plus lozenge
            - 33.2% bupropion plus lozenge
            - 34.4% patch alone
            - 33.5% lozenge alone
            - 31.8% bupropion alone
            - 22.2% placebo
    - in intention–to–treat analyses adjusted for multiple comparisons
        - interventions statistically superior to placebo at 8 weeks were
            - patch plus lozenge
            - bupropion plus lozenge
            - patch alone
        - only patch plus lozenge was statistically superior to placebo at 6 months
        - no significant differences comparing patch plus lozenge vs. other active interventions at 6 months
    - Reference – Arch Gen Psychiatry 2009 Nov;66(11):1253
- **combination therapy with nicotine lozenge plus either nicotine patch or bupropion may increase quit rates compared to monotherapies (level 2 [mid–level] evidence)**
    - based on randomized trial without blinding
    - 1,504 smokers randomized to 1 of 5 active smoking cessation treatments
        - bupropion up–titrated for 1 week before quitting to 150 mg twice daily and continued for postquit weeks 1–8
        - nicotine patch 21 mg for postquit weeks 1–4, 14 mg for weeks 5–6, and 7 mg for weeks 7–8

        - nicotine lozenge 2–4 mg (based on dose-for-dependence level instructions) 1 lozenge every 1–2 hours for postquit weeks 1–6, 1 lozenge every 2–4 hours for weeks 7–9, and 1 lozenge every 4–8 hours for weeks 10–12
        - combination of lozenge plus bupropion
        - combination of lozenge plus patch
    - telephone cessation counseling was available to all participants
    - 1,346 patients picked up study drugs, 90% completed study
    - smoking status assessed by self-report in telephone interviews
    - abstinence rates at 8 weeks
        - 45.5% lozenge plus bupropion ($p < 0.001$ vs. each monotherapy)
        - 44.8% lozenge plus patch ($p < 0.001$ vs. each monotherapy)
        - 17.7% patch alone
        - 28% lozenge alone
        - 27.7% bupropion alone
    - abstinence rates at 6 months
        - 29.9% lozenge plus bupropion ($p < 0.001$ vs. bupropion alone and vs. patch alone, $p = 0.005$ vs. lozenge alone)
        - 26.9% lozenge plus patch ($p = 0.004$ vs. bupropion alone, $p = 0.006$ vs. patch alone, $p = 0.06$ vs. lozenge alone)
        - 28.4% patch alone
        - 19.9% lozenge alone
        - 16.8% bupropion alone
    - Reference – Arch Intern Med 2009 Dec 14;169(22):2148

Nicotine patch plus oral inhaler:

- **addition of nicotine patch to nicotine inhaler may improve short-term quit rates (level 2 [mid-level] evidence)**
    - based on randomized trial with high dropout rate
    - 400 patients who smoked ≥ 10 cigarettes/day for ≥ 3 years were randomized to nicotine inhaler plus nicotine patch vs. nicotine inhaler plus placebo patch
        - nicotine inhaler given for 26 weeks
        - nicotine patch given as nicotine 15 mg/16 hours for 6 weeks then placebo patch for 6 weeks (placebo patch for 12 weeks in placebo group)

    - follow-up rates 74% at 6 weeks, 55% at 12 weeks, 33% at 6 months and 24% at 1 year
    - abstinence rates comparing nicotine patch vs. placebo patch
        - 60.5% vs. 47.5% at 6 weeks (p = 0.009, NNT 8)
        - 42% vs. 31% at 12 weeks (p = 0.02, NNT 9)
        - 25% vs. 22.5% at 6 months (not significant)
        - 19.5% vs. 14% at 1 year (not significant)
    - Reference – Arch Intern Med 2000 Nov 13;160(20):3128 full-text
- **addition of nicotine inhaler and bupropion to nicotine patch may improve abstinence rates in medically ill smokers (level 2 [mid-level] evidence)**
    - based on randomized trial without blinding
    - 127 smokers ≥ 18 years old with medical illness randomized to combination of nicotine patch plus nicotine oral inhaler plus bupropion vs. nicotine patch alone and followed for 26 weeks after quit date
    - medical illnesses included cardiovascular disease, other vascular disease, chronic pulmonary disease, cancer, hypertension, diabetes, hyperlipidemia, and recurrent pulmonary infections
    - comparing combination therapy vs. nicotine patch
        - abstinence at 26 weeks in 35% vs. 19% (p = 0.04, NNT 7)
        - median time to relapse 65 days vs. 23 days (p = 0.005)
        - insomnia in 25% vs. 9%
        - anxiety in 22% vs. 3%
    - Reference – Ann Intern Med 2009 Apr 7;150(7):447, editorial can be found in Ann Intern Med 2009 Apr 7;150(7):496

▼Comparative Efficacy

Comparisons of nicotine replacement products:

- various nicotine replacement therapies appear to be equally effective, but combination long-term nicotine patch therapy and *ad libitum* nicotine gum or spray may be more effective than any other single or combination NRT[1]
- **various types of nicotine replacement products appear equally efficacious for achieving short-term abstinence (level 2 [mid-level] evidence)**
    - based on randomized trial without sufficient power to rule out clinical differences

    - 504 volunteers smoking > 10 cigarettes/day and seeking help to quit randomized to nicotine polacrilex (gum) vs. transdermal patch vs. nasal spray vs. inhaler purchased at half price
    - continuous validated 12-week abstinence rates
        - nicotine polacrilex (gum) – 19.7%
        - transdermal patch – 21%
        - nasal spray – 23.8%
        - inhaler – 24.4%
    - compliance was high for patch, low for gum, very low for spray and inhaler
    - Reference – Arch Intern Med 1999 Sep 27;159(7):2033 full-text, commentary can be found in Arch Intern Med 2000 Jul 10;160(13):2062
- **nicotine patch and nasal spray have similar efficacy overall but patient characteristics might predict relative efficacy (level 2 [mid-level] evidence)**
    - based on subgroup analyses in randomized trial
    - 299 treatment-seeking smokers randomized to transdermal nicotine patch vs. nicotine nasal spray and followed for 6 months
    - no significant difference in overall abstinence rates at 6 months (15% with patch vs. 12.2% nasal spray)
    - transdermal nicotine had higher abstinence rates in smokers with low to moderate dependence levels, no obesity, and white ethnicity
    - nicotine nasal spray had higher abstinence rates in smokers who were highly dependent, obese, or members of minority group
    - Reference – Ann Intern Med 2004 Mar 16;140(6):426 PDF, commentary can be found in Am Fam Physician 2005 Feb 1;71(3):570
- **nicotine patch and lozenger had similar quit rates overall but lozengers had higher quit rates for smoking associated with stress (level 2 [mid-level] evidence)**
    - based on randomized trial without blinding
    - 642 patients seeking smoking cessation treatment randomized to transdermal nicotine patch vs. nicotine lozenger for 12 weeks
    - quit rate at 6 months 15.6% with patch vs. 10.9% with lozenge (not significant)
    - smokers using nicotine to alleviate stress or stimulate cognitive processes had higher quit rates with lozengers
    - Reference – Drug Alcohol Depend 2010 Mar 1;107(2-3):237

Nicotine vs. bupropion:

- **bupropion may be more effective than nicotine replacement (level 2 [mid-level] evidence)**
    - based on randomized trial with high dropout rate
    - treatment with sustained-release bupropion alone or in combination with nicotine patch resulted in significantly higher long-term rates of smoking cessation than either nicotine patch alone or placebo
    - study of 893 adults who smoked > 15 cigarettes/day, weighed at least 100 lbs (45.4 kg), and were motivated to quit smoking
    - exclusion criteria included clinical depression; serious cardiac, renal, hypertensive, pulmonary, endocrine or neurologic disorders; seizure or dermatologic disorders; history of panic disorder, psychosis, bipolar disorder or eating disorder; use of nicotine replacement therapy within 6 months, pregnancy or lactation, drug or alcohol abuse within 1 year, use of psychoactive drug within 1 week, any prior use of bupropion, current use of other smoking cessation treatments, regular use of any noncigarette tobacco product
    - patients randomized to
        - bupropion (Zyban 150 mg orally once daily for 3 days then twice daily)
        - placebo for 9 weeks and also randomized to nicotine-patch therapy (Habitrol 1 mg/day for weeks 2-7, 14 mg/day for week 8, 7 mg/day for week 9)
        - placebo
    - target quit day usually day 8, all patients assessed weekly and attended brief individual counseling session for smoking cessation weekly and supportive phone call about 3 days after target quit date, further assessments and relapse-prevention counseling occurred at 10, 12, 26 and 52 weeks plus phone calls from counselor at 3, 4, 5 and 7-11 months
    - 6-month abstinence rates were
        - 18.8% for placebo
        - 21.3% for nicotine patch (not significant)
        - 34.8% for bupropion (NNT 7)
        - 38.8% for combination therapy (NNT 5)

- 12-month abstinence rates were
  - 15.6% for placebo
  - 16.4% for nicotine patch (not significant)
  - 30.3% for bupropion (NNT 7)
  - 35.5% for combination therapy (NNT 5)
- 34.8% subjects discontinued treatment, but numbers presented based on intention-to-treat analysis assuming those who discontinued treatment were still smoking; those discontinuing therapy due to adverse events were
  - 3.8% placebo group
  - 6.6% nicotine patch group
  - 11.9% bupropion group (NNH 12)
  - 11.4% combination therapy group (NNH 13)
- average weight gain by week 7 was
  - 2.1 kg with placebo
  - 1.6 kg with nicotine patch
  - 1.7 kg with bupropion
  - 1.1 kg with combination therapy
- Reference – N Engl J Med 1999 Mar 4;340(9):685, commentary can be found in N Engl J Med 1999 Aug 19;341(8):610, ACP J Club 1999 Jul-Aug;131(1):13
- *DynaMed commentary* -- subjects in this trial all had frequent brief counseling support, another trial should determine the efficacy of this support
- subjects were volunteers, had weekly counseling and carbon monoxide testing; cessation rates may be lower in actual practice (J Fam Pract 1999 Jun;48(6):419), commentary regarding losses to follow-up can be found in J Fam Pract 1999 Oct;48(10):819

Nicotine vs. varenicline:

- **varenicline may increase continuous abstinence rates more than transdermal nicotine (level 2 [mid-level] evidence)**
  - based on randomized trial without blinding and with high dropout rate
  - 757 patients randomized to varenicline (uptitrated to 1 mg twice daily) for 12 weeks vs. transdermal nicotine (tapering from 21 mg/day to 7 mg/day) for 10 weeks

- 746 patients who took at least 1 dose of treatment medication were analyzed
- comparing varenicline vs. transdermal nicotine
  - confirmed continuous abstinence for last 4 weeks of treatment in 55.9% vs. 43.2% (p < 0.001, NNT 8)
  - confirmed continuous abstinence from treatment cessation through 52 weeks in 26.1% vs. 20.3% (p = 0.056)
  - nausea in 37.2% vs. 9.7% (NNH 3)
  - discontinuation rate during treatment phase 17.3% vs. 20.3%
  - discontinuation rate due to adverse events 3.5% vs. 1.6%
  - trial completion rate at 52 weeks 65.7% vs. 62.2%
- varenicline reduced craving, withdrawal symptoms and smoking satisfaction compared to nicotine replacement
- Reference – Thorax 2008 Aug;63(8):717 full-text, editorial can be found in Thorax 2008 Aug;63(8):666

▼Combinations with Other Drugs

Bupropion:

- **combination bupropion plus nicotine inhaler may be more effective than either monotherapy, bupropion appears more effective than nicotine inhaler (level 2 [mid-level] evidence)**
  - based on randomized trial with high dropout rates
  - 1,700 smokers (at least 10 cigarettes/day for at least 12 months) randomized to bupropion vs. nicotine inhaler vs. both for 3 months
    - bupropion sustained-release 300 mg daily
    - nicotine inhaler up to 16 cartridges/day
    - 671 (39%) dropped out before 3 months
    - comparing bupropion vs. nicotine inhaler vs. both at 3 months
      - 26% vs. 14% vs. 34% abstinent based on 7-day point prevalence (p < 0.001, NNT 5 for combination vs. nicotine, NNT 13 for combination vs. bupropion, NNT 9 for bupropion vs. nicotine)
      - 8% vs. 7% vs. 11% continuous abstinence (p = 0.02, NNT 25 for combination vs. nicotine, NNT 34 for combination vs. bupropion)

    - 405 abstinent smokers at 3 months randomized to continue initially assigned therapy vs. placebo for 9 months
        - 224 (55%) followed up at 12 months
        - continued treatment associated with lower relapse rates, but not statistically significant
    - 432 persistent smokers at 3 months (who were initially assigned monotherapy) randomized to alternative treatment vs. placebo for 3 months
        - 218 (50%) followed up at 12 months
        - among 222 smokers initially assigned nicotine inhaler, bupropion associated with increased likelihood of stopping smoking at 6 months (7% vs. 0, p = 0.003, NNT 15)
        - among 209 smokers initially assigned bupropion, nicotine inhaler did not significantly increase smoking cessation rates at 6 months (6% vs. 3%, p = 0.5)
    - Reference – Mayo Clin Proc 2007 Feb;82(2):186
- **addition of bupropion for 7 weeks appears NO more effective than placebo in patients taking nicotine replacement therapy and counseling (level 2 [mid-level] evidence)**
    - based on randomized trial with wide confidence intervals
    - 244 smokers were all treated with transdermal nicotine for 2 months and cognitive-behavioral counseling for 3 months and randomized to bupropion vs. placebo for 7 weeks
    - most participants were middle-aged white male veterans
    - quit rates comparing bupropion vs. placebo
        - self-reported quit rates at end of treatment (7 weeks) 64% vs. 57% (not significant)
        - self-reported quit rates at 12 weeks 57% vs. 47% (p = 0.13)
        - self-reported quit rates at 6 months 40% vs. 42% (not significant)
        - self-reported quit rates at 12 months 32% vs. 32% (not significant)
        - validated quit rates at 12 months 22% vs. 28% (not significant)
    - Reference – Arch Intern Med 2004 Sep 13;164(16):1797, commentary can be found in J Fam Pract 2004 Dec;53(12):953, Am Fam Physician 2005 Jan 15;71(2):347, Arch Intern Med 2005 Feb 28;165(4):470

Safety

- adverse effects of nicotine replacement include gastrointestinal upset and irritation based on route of application

- **varenicline, bupropion and nicotine replacement do not appear to be associated with different risks for self-harm (level 2 [mid-level] evidence)**
    - based on cohort study with inadequate statistical power
    - 80,660 men and women aged 18–95 years prescribed new course of smoking cessation product (nicotine replacement products, varenicline, or bupropion) followed from date of first prescription to 3 months after date of last prescription (for fatal or non-fatal self-harm)
    - events during follow-up
        - 166 episodes of non-fatal self harm (mostly self-poisoning)
        - 2 suicides (both in patients prescribed nicotine replacement products)
        - 37 episodes of suicidal thoughts
    - incidence of self harm (standardized for age and sex)
        - 533.1 per 100,000 person-years with varenicline
        - 498.7 per 100,000 person-years with bupropion
        - 751.7 per 100,000 person-years with nicotine replacement products
    - no significant differences in adjusted analyses in fatal and non-fatal self harm, in suicidal thoughts, or in starting antidepressant therapy
    - Reference – BMJ 2009 Oct 1;339:b3805 full-text, editorial can be found in BMJ 2009 Nov 5;339:b4360, commentary can be found in BMJ 2009 Dec 1;339:b4964 (commentary can be found in BMJ 2009 Dec 31;339:b5654)

- nicotine withdrawal can significantly alter metabolism of other substances, for example half-life of theophylline increases by 36% after smoking cessation and plasma caffeine levels increase by > 250% (N Engl J Med 1995 Nov 2;333(18):1196)
- **electronic cigarettes may contain carcinogens and toxic chemicals**
    - FDA sampled electronic cigarettes from 2 leading brands and found diethylene glycol and other carcinogens (including nitrosamines) in some samples

- electronic cigarettes are not FDA approved as nicotine replacement products
- Reference – FDA MedWatch 2009 Jul 22, FDA Press Release 2009 Jul 22

General population:

- **nicotine replacement therapy does not appear to acutely increase risk of myocardial infarction, stroke or death (level 2 [mid-level] evidence)**
  - based on observational study
  - 33,247 patients prescribed nicotine replacement therapy were evaluated
  - 861 had myocardial infarction, 506 had stroke
  - progressive increase in risk of myocardial infarction and stroke in 56 days preceding nicotine replacement therapy prescription but no increase in 56 days after nicotine replacement therapy prescription
  - 960 deaths during mean follow-up 2.6 years after nicotine replacement therapy prescription, no increased mortality in first 56 days
  - Reference – Tob Control 2005 Dec;14(6):416
  - *DynaMed commentary* –– increase in cardiovascular events prior to nicotine replacement therapy may be attributed to selection bias with patients having catastrophic events choosing to start nicotine replacement therapy

Patients with cardiac disease:

- NRT is not associated with increased cardiovascular risk, even in patients who continue to smoke[1]

- **transdermal nicotine may be safe in patients with cardiac disease but may not be particularly effective (level 2 [mid-level] evidence)**
  - based on randomized trial with allocation concealment not stated
  - 584 smokers with cardiovascular disease randomized to transdermal nicotine therapy vs. placebo for 10 weeks
  - no significant differences in
    - death
    - myocardial infarction (MI)

        - cardiac arrest
        - hospital admission for worsened heart disease
        - hospital admission for noncardiac disease
        - outpatient visits for worsened cardiac disease
        - smoking cessation at 24 weeks
        - side effects
    - advantage found for nicotine patch at 14 weeks
    - Reference – N Engl J Med 1996 Dec 12;335(24):1792 full-text, correction can be found in N Engl J Med 2007 Jun 14;356(24):2554, commentary can be found in N Engl J Med 1999 Oct 7;341(15):1157
- **nicotine patch used for smoking cessation reported to reduce exercise-induced myocardial ischemia in cigarette smokers with known CAD (level 3 [lacking direct] evidence)**
    - based on observational study in 36 patients without clinical outcomes
    - reduction in exercise-induced myocardial ischemia occurred despite increase in serum nicotine levels
    - Reference – J Am Coll Cardiol 1997 Jul;30(1):125
- review of nicotine replacement therapy and cardiovascular disease can be found in Mayo Clin Proc 2005 May;80(5):652 PDF

- **nicotine patch use not associated with increased risk for acute first myocardial infarction**
    - based on case-control study
    - Reference – J Am Coll Cardiol 2001 Apr;37(5):1297

Pregnancy:

- Pregnancy Category D
    - commentary regarding use of nicotine patch in pregnancy can be found in N Engl J Med 1999 Nov 25;341(22):1700
- **maternal nicotine replacement therapy (NRT) not associated with increased risk of stillbirth (level 2 [mid-level] evidence)**
    - based on cohort study of 87,032 women from Danish National Birth Cohort
    - 495 women with singleton pregnancies that ended in stillbirth
    - risk of still birth compared to non-smoking women who did not use NRT

        - hazard ratio 0.57 (95% CI 0.28–1.16) for women who used NRT during pregnancy
        - hazard ratio 1.46, (95% CI 1.17–1.82) for women who smoked during pregnancy
        - hazard ratio 0.83 (95% CI 0.34–2.00) for women who both smoked and used NRT
    - Reference – BJOG 2008 Oct;115(11):1405
- **nicotine gum in pregnancy associated with increase in birth weight and gestational age, but not smoking cessation rates compared with placebo (level 2 [mid-level] evidence)**
    - based on randomized trial without adequate statistical power
    - 194 pregnant daily smokers at ≤ 26 weeks gestation received individual behavior counseling for smoking cessation then randomized to nicotine gum 2 mg vs. placebo for 6 weeks, followed by a 6 week taper
        - if committed to a quit date, patients chewed nicotine gum or placebo in place of every cigarette typically smoked per day, not to exceed 20 pieces daily
        - if not committed to a quit date, patients substituted one piece of nicotine gum for each cigarette eliminated
    - comparing gum vs. placebo groups
        - reduction in cigarettes smoked per day −5.7 vs. −3.5 cigarettes ($p = 0.035$)
        - no significant difference in biochemically validated smoking cessation rates after 6 weeks
        - birth weight 3,287 g vs. 2,950 g ($p < 0.001$)
        - gestational age 38.9 weeks vs. 38 weeks ($p = 0.014$)
    - trial stopped early due to determination that much larger study needed to show increased quit rate benefit
    - at time of stopping, quit rate 14% with gum vs. 7 % with placebo
    - Reference – Obstet Gynecol 2008 Oct;112(4):859
- review of smoking cessation in pregnancy can be found in Expert Opin Drug Saf 2008 Nov;7(6):727
- review of smoking cessation in pregnancy can be found in Clin Obstet Gynecol 2008 Jun;51(2):419

Critical care:

- **nicotine replacement therapy associated with increased mortality in critically ill patients (level 2 [mid-level] evidence)**
    - based on cohort study
    - 90 smokers who received nicotine replacement therapy during intensive care unit stay were compared to 90 smokers who did not receive nicotine replacement therapy
    - 20% nicotine replacement therapy patients vs. 7% controls died in hospital (p = 0.0085, NNH 7)
    - Reference – Crit Care Med 2007 Jun;35(6):1517

▼References including Reviews and Guidelines

General references used:

- 1. Fiore MC, Jaen CR, Baker TB, et al; United States Department of Health and Human Services, Public Health Service. Clinical practice guideline: Treating tobacco use and dependence: 2008 update. DHHS 2008 May PDF or at National Guideline Clearinghouse 2008 May 12:12520, endorsed by American Academy of Pediatrics (Pediatrics 2008 Aug;122(2):471)
    - Public Health Service guideline panel Strength of Evidence ratings
        - Strength of Evidence A – multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings
        - Strength of Evidence B – some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optima
        - Strength of Evidence C – reserved for important clinical situations in which Panel achieved consensus on recommendation in the absence of relevant randomized controlled trials

Reviews:

- systematic review of smoking cessation pharmacotherapy can be found in BMC Public Health 2006 Dec 11;6:300 full-text
- evidence-based review of pharmacotherapy can be found in J Am Board Fam Pract 2002 Nov-Dec;15(6):489 PDF

- review of medications for smoking cessation can be found in Adv Stud Med 2003 Oct;3(9):507 PDF
- review of medications for smoking cessation can be found in West J Med 2002 Mar;176(2):131 (Am Fam Physician 2002 Aug 1;66(3):497)
- review of nicotine replacement therapy can be found in BMJ 2004 Feb 21;328(7437):454, correction can be found in BMJ 2004 Mar 20;328(7441):686
- review of nicotine replacement therapy and cardiovascular disease can be found in Mayo Clin Proc 2005 May;80(5):652
- review of nicotine replacement systems can be found in N Engl J Med 1995 Nov 2;333(18):1196

Guidelines:

- synthesis of 3 guidelines (PHS 2008, UMHS 2006, USPSTF 2009) on tobacco cessation can be found at National Guideline Clearinghouse 2010 Jan 4:TOBACCO10
- NICE guidance on bupropion and nicotine replacement therapy for smoking cessation can be found at NICE 2002 Mar:TA39

Patient Information

Patient information:

- handout from American Academy of Family Practice
- handout from Smokefree.gov

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