

Recommendations for Use of Combination Therapy in Tobacco Use Cessation April 2009

VHA Pharmacy Benefits Management Services, Medical Advisory Panel, Tobacco Use Cessation Technical Advisory Group, and Public Health Strategic Healthcare Group

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.

Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Effective treatments exist that can significantly increase rates of long-term abstinence and are supported by the 2008 United States Public Health Services Update of Clinical Practice Guidelines on the Clinical Treatment of Tobacco Use and Dependence (USPHS CPG). One such recommendation included in these guidelines is the use of combinations of first-line medications in patients who are willing to quit smoking.

Combination Nicotine Replacement Therapy (NRT) involves the use of a long acting nicotine formulation (patch) in combination with a short acting formulation (gum, lozenge, inhaler, or nasal spray). Combination NRT offers constant levels of nicotine replacement provided by the patch and prevents the onset of severe withdrawal symptoms while the short acting nicotine replacement delivers nicotine at a faster rate and is used as needed to control breakthrough cravings and withdrawal symptoms that may occur during potential relapse situations (i.e. after meals).

Varenicline is also an effective treatment that can increase rates of abstinence, however, in the VHA varenicline is a second line agent due to safety concerns. Refer to the Varenicline Criteria for Prescribing at:

<http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Criteria%20For%20Use/Varenicline%20Criteria%20for%20Prescribing.doc>

Alternatively, the combination of a nicotine patch with bupropion SR has also been shown to be more effective in increasing long term abstinence compared to either agent alone.

Recommendations

1. The USPHS CPG on the Clinical Treatment of Tobacco Use and Dependence recommends the following:

Certain combinations of first-line medications have been shown to be effective smoking cessation treatments. Therefore, clinicians should consider using these combinations of medications in patients willing to quit.

[Strength of Evidence = A (multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings).]

Effective combinations of medications are:

- Long-term (>14 weeks) nicotine patch (18-24 weeks in trials) + other NRT (gum, lozenge, spray*) as needed for a minimum of 26 weeks (up to 52 weeks in trials). Use beyond 52 weeks should be reviewed on a case-by-case basis.
- Nicotine patch (10 weeks) + nicotine inhaler* (12-26 weeks)
- Nicotine patch (10 weeks) + bupropion SR (12 weeks)

! Please Note: the least expensive combination therapy in the VHA is nicotine patch plus gum.

! *Nicotine spray and nicotine inhaler are currently non-formulary in the VHA and available only through the local non-formulary process.

2. In the VHA, the First-line therapies for smoking cessation on the National Formulary include

- Nicotine Patch
- Nicotine Gum
- Nicotine Lozenge
- Bupropion
- Combination Therapy as described above

See Table 1 for a summary of evidence from the USPHS Clinical Practice Guideline. See Table 2 for examples of smoking cessation therapies and estimated costs.

Evidence Summary

Table 1. Effectiveness and Abstinence Rates for Tobacco Use Cessation Therapies at 6 months (Comparison to placebo)

Pharmacotherapy Intervention	Estimated Abstinence Rate (95% CI)	Estimated Odds Ratio (95% CI)
Placebo	13.8	1.0
Bupropion SR	24.2 (22.2-26.4)	2.0 (1.8-2.2)
Nicotine Gum (6-14wks)	19.0 (16.5-21.9)	1.5 (1.2-1.7)
Nicotine Gum (>14 wks)	26.1 (19.7-33.6)	2.2 (1.5-3.2)
Nicotine Lozenge (2mg)	24.2 ^a	2.0 (1.4-2.8)
Nicotine Patch (6-14 wks)	23.4 (21.3-25.8)	1.9 (1.7-2.2)
Varenicline (1mg)	25.4 (19.6-33.6)	2.1 (1.5-3.0)
Varenicline (2mg)	33.2 (28.9-37.8)	3.1 (2.5-3.8)
Nicotine Patch (18-24wks) + prn NRT (gum, lozenge, spray x 26-52 wks)	36.5 (28.6-45.3)	3.6 (2.5-5.2)
Nicotine Patch + Bupropion SR	28.9 (23.5-35.1)	2.5 (1.9-3.4)
Nicotine Patch + Nortriptyline	27.3 (17.2-40.4)	2.3 (1.3-4.2)
Nicotine Patch + Nicotine Inhaler	25.8 (17.4-36.5)	2.2 (1.3-3.6)

^aOne qualifying randomized trial; 95% CI not reported

Odds Ratio: Ratio of the odds of having an outcome when exposed to one variable (i.e. odds of quitting smoking among those receiving the medication) compared with the odds of the outcome when not exposed to the variable (i.e. odds of quitting smoking among those who did not receive the medication).

- All combination therapies more than doubled the likelihood of helping smokers achieve long term abstinence when compared to placebo
- When compared to nicotine patches, only the 2mg varenicline and the combination of long-term patch plus as needed NRT (gum or spray) were found to have abstinence rates significantly better than patches alone. (Odds ratio for varenicline alone and the combination of patch plus gum or spray: 1.6 and 1.9, respectively).
- The combination of patch and long term gum/lozenge/spray more than tripled the likelihood of long term abstinence and was associated with a significantly greater likelihood of abstinence compared to nicotine patch alone. This is comparable to the effects seen with varenicline (2mg/day).

Dosing and Cost

- Dosing recommendations varied in studies; Experts have suggested the following dosing guidelines: Dose the patch as described (21mg or 14 mg based on daily cigarette usage). Prescribe adjunct NRT products on an as needed basis when acute withdrawal symptoms and urges to use tobacco occur. Adjust dose of patch if frequent use of other NRT; goal is to minimize need for PRN dosing. In general, longer durations (as listed in Table 2) are indicated for heavier smokers or those who are having difficulty achieving abstinence.

Table 2. Price Comparisons of Combination Therapy

Medication(s)	Regimen	Price per Dose ^a	Price per Patient per Month ^a
Nicotine Inhaler	6-16 cartridges/day; use 1 cartridge at a time; individualize dose	\$0.47	\$79.28 (6 cartridges/day); duration: up to 6 months
Nicotine Nasal Spray	1-2 doses/hr (8-40 doses/day)	\$0.20	\$80.30 (14 doses/day); duration: 3-6 months
Nicotine Patch	21mg/d x 4-6 weeks then 14mg x 2 weeks then 7mg x 2 weeks	\$1.37	\$41.32 (all strengths; 1 patch/day); duration: 2-3 months
Nicotine Gum	1 piece q1-2hrs x 6 weeks 1 piece q2-4hrs x 3 weeks 1 piece q4-8hrs x 2 weeks	2mg: \$0.14/piece 4mg: \$0.16/piece	\$32.18 (2mg; 7.3 pieces/day) \$36.22 (4mg; 7.3 pieces/day) duration: up to 3 months
Nicotine Lozenge	1 piece q1-2hrs x 6 weeks 1 piece q2-4hrs x 3 weeks	2mg and 4mg:	\$49.08 (all strengths; 5 pieces/day)

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Updated versions may be found at <http://www.pbm.va.gov> or <http://vaww.pbm.va.gov>

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	1 piece q4-8hrs x 2 weeks	\$0.35/piece	duration: up to 3 months
Bupropion SR	150mg twice daily	\$0.25	\$15.08 duration: 2-3 months
Varenicline	1mg twice daily	0.5mg and 1mg: \$1.17	\$70.20 duration: 3-6 months
Nicotine Patch + prn NRT (gum, lozenge, spray)	21mg/d x 6 weeks 14mg x 6 weeks 7mg x 6 weeks + prn NRT x 26-52 weeks	\$1.37/day + Varies (per dose and daily cost varies depending on agent and PRN usage/day)	\$41.32+ \$16.80 (4 pieces gum/day)=\$58.12 \$41.32+\$42 (4 lozenge/day)=\$83.32 \$41.32 + \$48 (8 doses spray/day)=\$89.32; duration: 4-6 months (patch); up to 6-12 months (prn NRT)
Nicotine Patch + Bupropion SR	21mg/d x 6 weeks then 14mg x 2 weeks then 7mg x 2 weeks + 150mg twice daily x 12 weeks	\$1.37/day + \$0.50/day	\$56.40 duration: 2-3 months
Nicotine Patch + Nicotine Inhaler	21mg/d x 6 weeks then 14mg x 2 weeks then 7mg x 2 weeks + 6-16 cartridges/day	\$1.37/day + \$0.47/dose (per dose and daily cost varies depending on agent and PRN usage)	\$41.32 + \$79.28 (6 cartridges/day) = \$120.60 duration: 3-9 months

^a Based on current Federal Supply Schedule, BIG4 or VA Contract Price

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Schneider NG, Cortner C, Gould JL, Koury MA, Olmstead RE. Comparison of craving and withdrawal among four combination nicotine treatments. *Hum Psychopharmacol*. 2008 Aug;23(6):513-7

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Appendix A

Clinical Trial Data

Trial	Patient Population	N	Treatment	Results																				
Blondal et al. 1999	Current smokers aged 22-66.	237	Nicotine patch x 5 weeks + nicotine nasal spray x 52 weeks (n=120) vs. nicotine patch + placebo spray (n=119) (Patch dose: 15 mg of nicotine for 3 months, 10 mg for the fourth month, and 5 mg for the fifth month)	<p>Abstinence Rates</p> <table border="1"> <thead> <tr> <th>Time point</th> <th>Patch + Spray</th> <th>Patch + placebo spray</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>Wk 6</td> <td>51%</td> <td>35%</td> <td>0.011</td> </tr> <tr> <td>Wk12</td> <td>37%</td> <td>25%</td> <td>0.045</td> </tr> <tr> <td>Month 6</td> <td>31%</td> <td>16%</td> <td>0.005</td> </tr> <tr> <td>Month 12</td> <td>27%</td> <td>11%</td> <td>0.001</td> </tr> </tbody> </table> <p>Six-year survival analysis showed a significant association between abstinence and treatment with nicotine inhaler + patch ($X^2= 8.5, P =.004$). 13% of subjects still used nicotine nasal spray at the 12 month time point.</p>	Time point	Patch + Spray	Patch + placebo spray	p value	Wk 6	51%	35%	0.011	Wk12	37%	25%	0.045	Month 6	31%	16%	0.005	Month 12	27%	11%	0.001
Time point	Patch + Spray	Patch + placebo spray	p value																					
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Bohadana et al. 2000	Current smokers: smoked 10 or more cigarettes per day for 3 years or longer	400	Group 1 (n = 200) received nicotine inhaler (6-12 cartridges/day) + nicotine patch (15mg) for 6 weeks, then inhaler + placebo patch for 6 weeks, then inhaler alone for 14 weeks (tapering dose). Group 2 (n = 200) received nicotine inhaler + placebo patch for 12 weeks, then inhaler for 14 weeks (6 to 12 cartridges per day ad libitum for 3 months and then tapered off).	<p>Abstinence Rates</p> <table border="1"> <thead> <tr> <th>Time point</th> <th>Group 1</th> <th>Group 2</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>Wk 6</td> <td>121 (60.5%)</td> <td>95 (47.5%)</td> <td>0.009</td> </tr> <tr> <td>Wk12</td> <td>84 (42%)</td> <td>62 (31.0%)</td> <td>0.02</td> </tr> <tr> <td>Month 6</td> <td>50 (25%)</td> <td>45 (22.5%)</td> <td>0.56</td> </tr> <tr> <td>Month 12</td> <td>39 (19.5%)</td> <td>28 (14%)</td> <td>0.14</td> </tr> </tbody> </table> <p>One-year survival analysis showed a significant association between abstinence and treatment with nicotine inhaler + patch ($X^2= 4.11, P =.04$). Mean inhaler use/day was 4.41±2.53 in Group 1 with no increase in inhaler use after 6 weeks.</p>	Time point	Group 1	Group 2	p value	Wk 6	121 (60.5%)	95 (47.5%)	0.009	Wk12	84 (42%)	62 (31.0%)	0.02	Month 6	50 (25%)	45 (22.5%)	0.56	Month 12	39 (19.5%)	28 (14%)	0.14
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Croghan et al. 2003	Current smokers with Cancer	1384	Nicotine patch (n=459) vs. nicotine spray (n=463) vs. patch + spray (n=462); no counseling	6 week (7-day point prevalence) abstinence rates: patch alone (21.1%), spray alone (13.6%), patch + spray (27.1%) (p=0.025 patch vs combination). 6 months (7-day point prevalence) abstinence rates: patch alone (7.8%), spray alone (6.9%), patch + spray (9.1%) (p=0.554)																				
George, et al. 2008	DP, PC, in smokers with schizophrenia	58	Bupropion SR + nicotine patch (n=29) vs. placebo + patch (n=29)	6-months: 13.8% versus 0% achieved 7-day point prevalence smoking abstinence (p = .11)																				
Jamerson, et al. 2001	Post hoc analysis of multicenter, DB, RCT of current heavy smokers	893	placebo (n = 160), bupropion SR (n = 244), nicotine patch (n = 244), or nicotine patch + bupropion SR (n = 245) x 9 weeks	successful smoking cessation rates: weeks 4 to 9 - 19% bupropion SR or combination, 7% nicotine patch, 7% placebo month 6 -13% combination, 11% bupropion SR, 2% nicotine patch, 3% placebo month 12- 10% bupropion SR, 7% combination, 2% nicotine patch, 1% placebo (P < 0.05 for bupropion SR and combination vs nicotine patch or placebo).																				
Jorenby et al. 1999	DB, placebo controlled of current smokers. (those with depression were excluded)	893	sustained-release bupropion (n=244) vs nicotine patch (n= 244), vs. bupropion + nicotine patch (n=245), vs. placebo (n= 160) x 9weeks (patch regimen: 21 mg/day x 6 wks, 14 mg/day x 1 wk, and 7 mg/day x1wk)	<p>Abstinence Rates at 12 months</p> <table border="1"> <thead> <tr> <th>Time point</th> <th>placebo</th> <th>Patch</th> <th>Buproion SR</th> <th>Patch + bup SR</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>1 Yr</td> <td>15.6%</td> <td>16.4%</td> <td>30.3%</td> <td>35.4%</td> <td><0.001</td> </tr> </tbody> </table> <p>Weight gain was significantly less in the combination therapy group (P<0.05)</p>	Time point	placebo	Patch	Buproion SR	Patch + bup SR	p value	1 Yr	15.6%	16.4%	30.3%	35.4%	<0.001								
Time point	placebo	Patch	Buproion SR	Patch + bup SR	p value																			
1 Yr	15.6%	16.4%	30.3%	35.4%	<0.001																			
Kornitzer et al. 1995	DB, randomized placebo-controlled trial in healthy smokers using >10 cigarettes/day	374	nicotine patch + gum (group 1; n=149), nicotine patch + placebo gum (group 2; n=150), placebo patch + gum (group 3; n=75)	<p>Abstinence Rates</p> <table border="1"> <thead> <tr> <th>Time point</th> <th>Grp 1</th> <th>Grp 2</th> <th>Grp 3</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>Wk12</td> <td>34.2%</td> <td>22.7%</td> <td>17.3%</td> <td>0.027</td> </tr> <tr> <td>Month 6</td> <td>27.5%</td> <td>15.3%</td> <td>14.7%</td> <td>0.01</td> </tr> </tbody> </table>	Time point	Grp 1	Grp 2	Grp 3	p value	Wk12	34.2%	22.7%	17.3%	0.027	Month 6	27.5%	15.3%	14.7%	0.01					
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			Patch regimen: 15mg x 12wks, 10mg x 6wks, 5mg x 6 wks; recommended gum use =at least 4pieces/day	<table border="1"> <tr> <td>Month 12</td> <td>18.1%</td> <td>12.7%</td> <td>13.3%</td> <td>0.19</td> </tr> </table> <p>Subjects in Grp 1 were significantly more likely to achieve abstinence at all measured time points (p<0.1)</p>	Month 12	18.1%	12.7%	13.3%	0.19							
Month 12	18.1%	12.7%	13.3%	0.19												
Prochazka, et al. 2004	R, DB, PC of smokers aged 18-65 yrs using >10 cigarettes/day and no major depression	158	Nortriptyline 25 mg 14 days before quit day, titrated to 75 mg/d as tolerated, x 12 weeks + Nicotine patch (21 mg/d) x 8 weeks (n=79) vs. placebo + nicotine patch (n=79)	<p>Abstinence Rates</p> <table border="1"> <thead> <tr> <th>Time point</th> <th>Nortriptyline + Patch</th> <th>Placebo + Patch</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>Month 6</td> <td>23%</td> <td>10%</td> <td>0.052</td> </tr> </tbody> </table> <p>Nortriptyline caused frequent side effects, including dry mouth (38%) and sedation (20%)</p>	Time point	Nortriptyline + Patch	Placebo + Patch	p value	Month 6	23%	10%	0.052				
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Puska, et al. 1995	Randomized, double blind	300	Nicotine gum (2mg) (n=150) vs. nicotine patch + gum (2mg pm) (n=150) Patch regimen: 15mg x 12wks, 10mg x 3wks, 5mg x 3 wks;	<p>Abstinence Rates</p> <table border="1"> <thead> <tr> <th>Time point</th> <th>Gum</th> <th>Patch + gum</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>Wk12</td> <td>28%</td> <td>39.3%</td> <td><0.01</td> </tr> <tr> <td>Month 6</td> <td>17%</td> <td>24%</td> <td>NS</td> </tr> </tbody> </table>	Time point	Gum	Patch + gum	p value	Wk12	28%	39.3%	<0.01	Month 6	17%	24%	NS
Time point	Gum	Patch + gum	p value													
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Schneider et al. 2008	Current smokers	27	2 mg/4 mg gums + 15 mg patch, 2 mg/4 mg lozenges + 15 mg patch, inhalers + 15 mg patch, and 10 + 15 mg double patch	"Urge to smoke" and "total withdrawal" showed a rise from baseline to NRT use for the double patch but not for the three acute NRT + patch conditions. Lozenge/patch scores did not rise from baseline for "craving" and "miss a cigarette" but did for gum/patch, inhaler/patch, and double patch. The best relief occurred for NRTs of choice.												
Schneider et al. 2006	Current smokers	27	2/4-mg gum + 15-mg patch (G/P), 2/4-mg lozenges + 15-mg patch (L/P), inhaler + 15-mg patch (I/P), and 10 mg + 15-mg patches (P/P).	Double-patches (P/P) were ranked highest for "ease of use", "safety", and "use in public". For "help to quit", 70% preferred some form of acute-patch combination (A/P) compared to 30% choosing P/P. For "use under stress" (an immediate need), 93% preferred A/P systems compared to 7% choosing P/P.												
Shah et al. 2008	Systematic review and Meta-analysis; Trials conducted from 1994 through October 10, 2007. double-blind, randomized, placebo-controlled design; and study duration of 1 year or more; 5 studies included	2204	nicotine replacement patch along with one other agent	Combination therapy was significantly better than monotherapy at all pooled comparisons (P < 0.05). The aggregated relative risk of abstinence comparing combination with single treatment groups was 1.42 (95% CI 1.21-1.67), 1.54 (1.19-2.00), and 1.58 (1.25-1.99) at 3, 6, and 12 months												
Stead, et al 2008	Cochrane Review; 7 studies	3202	Combination NRT (n=1330) vs. single NRT (n=1763) (6 studies) Combination NRT vs. no NRT (n=109) (1 study)	Significant benefit of combination therapy over single NRT: RR=1.35 (95%CI 1.11-1.63)												
Swanson, et al. 2003	RCT	140	Bupropion SR vs. nicotine patch vs. combination nicotine patch + bupropion	12 month abstinence rates: nicotine patch + bupropionSR =27%, nicotine patch =20% , and bupropion SR = 7%												
Tonnesen P, et al. 2000	Open, randomized trial of smokers using >9 cigarettes/day in a low-resource lung clinic	446	5-mg nicotine patch (n=109) vs. 15-mg nicotine patch (n=104) vs. nicotine inhaler (n=118) vs. 15-mg nicotine patch + nicotine inhaler (n=115) (4-12 cartridges/day) x 3-9 months	12-month abstinence rates: 5-mg patch=6%, 15-mg patch= 16% (p<0.05), inhaler=9%, 15-mg patch + inhaler =11%												

CI=confidence interval; DB=double-blind; N=number of patients; NR=not reported; PC = placebo controlled; R=randomized; RR=relative risk; yrs=years

Contact Person: Mark Geraci Pharm.D., BCOP or Pam Belpario, Pharm.D.