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Combination nicotine replacement therapy: strategies for initiation and tapering

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### Authors

Hsia, SL  
Myers, MG  
Chen, TC

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1 **Title page**

2

3 Combination nicotine replacement therapy: dosing guidance and recommendations

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5 **Authors**

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7 Stephanie L. Hsia, PharmD<sup>a</sup>

8 Mark G. Myers, PhD<sup>a,b</sup>

9 Timothy C. Chen, PharmD<sup>a,b</sup>

10

11 <sup>a</sup>VA San Diego Healthcare System (VASDHS), 3350 La Jolla Village Drive (119), San Diego,  
12 California, USA 92161 [stephanie.hsia@va.gov] [timothy.chen@va.gov]

13 <sup>b</sup>Department of Psychiatry, University of California, San Diego, 9500 Gillman Drive, MC 0603,  
14 La Jolla, California, USA 92093. [mgmyers@ucsd.edu][tic072@ucsd.edu]

15

16 **Corresponding author**

17

18 Stephanie L. Hsia, PharmD

19 Email: stephanie.hsia@va.gov

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28 nicotine lozenge; combination nicotine; NRT; combination NRT

29 **Abstract**

30 Several studies and meta-analyses have demonstrated the efficacy of combination nicotine  
31 replacement therapy (NRT) for patients who wish to quit smoking. However, there is limited  
32 guidance with respect to dosing and tapering of combination NRT. We attempt to review the  
33 evidence and rationale behind combination NRT, present the dosing used in combination NRT  
34 studies, and propose a step-down approach for dosing and tapering of combination NRT with  
35 integration of behavioral strategies.

36

37 **Problem**

38 Though the prevalence of smoking in adults has decreased to approximately 15%, cigarette  
39 smoking remains a major public health concern.<sup>1</sup> In 2010, 52% of smokers made a quit attempt,  
40 and 32% used medications or counseling during their quit attempt.<sup>2</sup> The current U.S. Preventive  
41 Services Task Force (PSTF) and Public Health Service (PHS) smoking cessation  
42 recommendations state that combination nicotine replacement therapy (NRT) improves cessation  
43 success compared to monotherapy NRT.<sup>3-4</sup> Though the proportion of patients on combination  
44 NRT has increased since publication of these guidelines, there remains limited guidance for  
45 dosing and tapering of these combinations.<sup>5-6</sup>

46

47 **Rationale and Evidence**

48 Nicotine addiction is comprised of behavioral and physiological dependence; both should be  
49 addressed to help a patient remain tobacco-free. While behavioral interventions reduce the  
50 psychological dependence on nicotine, pharmacotherapy reduces the physiological dependence.<sup>3-</sup>  
51 <sup>4,6-8</sup> The rationale behind combination NRT is that long-acting and short-acting NRT target  
52 different cravings.<sup>6</sup> Long-acting NRT (e.g., patch) reduces overall nicotine dependence  
53 (background cravings) by providing a steady amount of nicotine to reduce withdrawal. Short-  
54 acting NRT (e.g., lozenge) relieves breakthrough cravings and provides sensory stimulation,  
55 which prevents lapses.<sup>6,9</sup> Since the absorption of nicotine is slower from NRTs than cigarettes,  
56 NRTs are less likely to cause dependence/addiction while still reaching sufficient concentrations  
57 to alleviate withdrawal symptoms.<sup>10-11</sup> Studies and meta-analyses have demonstrated that  
58 combination NRT improves abstinence rates with a similar incidence of adverse effects  
59 compared to monotherapy.<sup>6, 12-19</sup>

**Abbreviations**

NRT: nicotine replacement therapy; PSTF: Preventive Services Task Force; PHS: Public Health Service; HSI: Heaviness of Smoking Index

60

61 **Dosing in Published Studies**

62 Dosing strategies of combination NRT, which are summarized in Table 1, vary between studies.<sup>6,</sup>

63 <sup>12-19</sup>

64

**Abbreviations**

NRT: nicotine replacement therapy; PSTF: Preventive Services Task Force; PHS: Public Health Service; HSI: Heaviness of Smoking Index

65 **Table 1.** Summary of combination NRT dosing utilized in randomized, controlled trials.<sup>6, 12-19</sup>

Study	Nicotine Patch Dosage	Nicotine Gum, Lozenge, Spray Dosage
Kornitzer 1995	<ul style="list-style-type: none"> <li>• 15mg/16 hr x 12 weeks</li> <li>• 10mg /16 hr x 6 weeks</li> <li>• 5mg/16 hr x 6 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Gum (strength not reported)</li> <li>• At least 4 pieces/day x 12 weeks</li> </ul>
Puska 1995	<ul style="list-style-type: none"> <li>• 15mg/16 hrs x 12 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Gum (2mg)</li> <li>• At least 4 pieces/day</li> </ul>
Blondal 1999	<ul style="list-style-type: none"> <li>• 15mg x 3 months</li> <li>• Wean over 2 months</li> </ul>	<ul style="list-style-type: none"> <li>• Nasal spray</li> <li>• 0.5mg/dose x 1 year</li> </ul>
Bohadana 2000	<ul style="list-style-type: none"> <li>• 15mg/16 hr x 6 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Inhaler 4mg/cartridge</li> <li>• 6-12 cartridges/day x 3 months</li> </ul>
Croghan 2003	<ul style="list-style-type: none"> <li>• 15mg/16 hr x 6 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Nasal spray 0.5 mg/dose</li> <li>• 6 weeks</li> <li>• Max: 5 doses/hr, 40 doses/day</li> </ul>
Cooney 2009	<ul style="list-style-type: none"> <li>• 21mg/24 hr x 8 weeks</li> <li>• 14mg/24 hr x 2 weeks</li> <li>• 7mg/24hr x 2 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Gum (2mg)</li> <li>• At least 6 pieces/day x 24 weeks</li> <li>• Max: 20 pieces/day</li> </ul>
Piper 2009	<ul style="list-style-type: none"> <li>• 21mg/24 hr</li> <li>• 14mg/24 hr</li> <li>• 7mg/24 hr</li> <li>• Tapered down over 8 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Lozenge (2mg/4mg)<sup>a</sup></li> <li>• 12 weeks</li> </ul>
Smith 2009	<ul style="list-style-type: none"> <li>• 21mg/24 hr x 4 weeks</li> <li>• 14mg/24 hr x 2 weeks</li> <li>• 7mg/24 hr x 2 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Lozenge (2mg/4mg)<sup>a</sup></li> <li>• 1 lozenge Q1-2 hrs x 6 weeks</li> <li>• 1 lozenge Q2-4 hrs x 2 weeks</li> <li>• 1 lozenge Q4-8 hrs x 2 weeks</li> </ul>
Schlam 2016	<ul style="list-style-type: none"> <li>• 21mg/24 hr x 22 weeks if smoking &gt; 9 cigarettes/day</li> <li>• 21mg/24 hr x 4 weeks if smoking 5-9 cigarettes/day</li> <li>• 14mg/24 hr x 2 weeks</li> <li>• 7mg/24 hr x 2 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Gum (2mg/4mg)<sup>a</sup></li> <li>• 1 piece Q1-2 hrs</li> <li>• At least 5 pieces/day</li> </ul>
Baker 2016	<ul style="list-style-type: none"> <li>• If smoking &gt; 10 cigarettes/day               <ul style="list-style-type: none"> <li>○ 21mg/24 hr x 8 weeks</li> <li>○ 14 mg/24 hr x 2 weeks</li> <li>○ 7mg/24 hr x 2 weeks</li> </ul> </li> <li>• If smoking 5-10 cigarettes/day               <ul style="list-style-type: none"> <li>○ 14mg/24 hr x 10 weeks</li> <li>○ 7mg/24 hr x 2 weeks</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Lozenge (2mg/4mg)<sup>a</sup></li> <li>• At least 5 lozenges/day x 12 weeks</li> </ul>

66 <sup>a</sup>Participants received 4mg if they smoked within 30 minutes of waking and 2mg otherwise

67

68

## 69 **Dosing Recommendations, Tapering Strategies, and Behavioral Interventions**

70 Based on the favorable evidence, pharmacology, and safety of combination NRT, we suggest  
71 that the following regimen be initiated in patients with low to high nicotine dependence who  
72 want to quit smoking. Though this dosing strategy has not yet been validated, it is based off of  
73 evidence-based strategies from randomized controlled trials demonstrating the efficacy of  
74 combination NRT compared to monotherapy.<sup>6,12-19</sup> This tapering strategy was developed by the  
75 Tobacco Cessation Clinical Resource Center (TCCRC) at the Veterans Affairs San Diego  
76 Healthcare System (VASDHS) and is now widely used within the Veterans Health  
77 Administration (VHA).<sup>20</sup> Due to its relapsing nature, tobacco dependence should be treated like  
78 any other chronic disease. Patients should be followed on a long-term basis, and educated that  
79 reaching their goal requires incorporation of behavioral strategies with pharmacotherapy.<sup>3-4, 21-22</sup>

80

### 81 *Behavioral Interventions*

82 The U.S. PHS and PSTF guidelines recommend that patients receive counseling and medication  
83 since the combination of both is more effective than either intervention alone.<sup>3,4</sup> Because learned  
84 behaviors and environmental triggers comprise a significant component of nicotine dependence,  
85 behavioral interventions which target conditioned behaviors and situational triggers are  
86 necessary to help patients remain tobacco-free.<sup>7</sup> Patients may receive behavioral counseling  
87 through group, individual, or telephone settings, which should be integrated with  
88 pharmacotherapy. Furthermore, studies have shown a dose dependent relationship between  
89 number and intensity of counseling sessions and cessation rates. Guidelines recommend that  
90 patients receive at least four in-person or three telephone counseling sessions.<sup>3-4</sup> As with any  
91 chronic disease state (e.g., diabetes), behavioral interventions should be reinforced often and  
92 continued long-term.

93

### 94 *Selecting a Short-Acting Formulation of NRT*

95 The formulations of short-acting NRT with evidence are nicotine gum, lozenge, nasal spray, and  
96 oral inhaler, which differ in their pharmacokinetics and method of use. The nasal spray is more  
97 rapidly absorbed and eliminated than other forms, resulting in higher peak and lower trough  
98 nicotine concentrations.<sup>6</sup> Though this may alleviate cravings faster, it also perpetuates  
99 physiological dependence on nicotine, albeit still at lower levels than a cigarette.<sup>6, 11</sup> The nicotine

100 inhaler has the advantage of providing sensory stimulation (hand-to-mouth action), which may  
101 relieve cue-induced cravings. Although this may be beneficial initially, it reinforces smoking  
102 habits, which prolongs behavioral dependence on nicotine. Since the nasal spray and inhaler may  
103 prolong physiological and behavioral dependence on cigarettes, they are not preferred first-line  
104 options. However, the nicotine spray and inhaler are safe and may be preferred in certain patients  
105 such as those who fail treatment with the gum/lozenge or who are unable to use oral NRT (poor  
106 dentition, severe gastrointestinal disorders, etc.).<sup>8</sup> Patient preference should also be a factor in  
107 selecting a formulation as they may have differing side effects and costs.<sup>4</sup> We do not currently  
108 recommend the use of electronic cigarettes due to inconclusive evidence regarding the efficacy  
109 and safety of these devices for smoking cessation.<sup>23</sup>

110

#### 111 *Dosing Recommendations*

112 Initial dosages of combination NRT should be based on the patient's nicotine dependence, which  
113 may be assessed using the Heaviness of Smoking Index [(HSI) Table 2], an abbreviated and  
114 validated version of the Fagerström Test for Nicotine Dependence.<sup>24-25</sup>

115

116 **Table 2.** Heaviness of Smoking Index (HSI) for nicotine dependence.<sup>24-25</sup>

<b>Heaviness of Smoking Index (HSI)</b>	
How soon after waking do you smoke your first cigarette?	Less than 5 minutes (3 points)
	5-30 minutes (2 points)
	31-60 minutes (1 point)
	More than 60 minutes (0 points)
How many cigarettes do you smoke each day?	More than 30 cigarettes (3 points)
	21-30 cigarettes (2 points)
	11-20 cigarettes (1 point)
	10 cigarettes or less (0 points)
Nicotine dependence score	0 points: No dependence
	1-2 points: Low dependence
	3-4 points: Moderate dependence
	5-6 points: High dependence

117  
 118 Theoretically, serum nicotine concentrations produced by the 21mg/day patch may be lower than  
 119 those after heavy smoking (i.e., more than 30 cigarettes per day).<sup>26</sup> However, studies utilizing  
 120 high-dose nicotine patch (i.e., 42mg/day) in high dependency smokers have yielded conflicting  
 121 results and lack sound safety data given their significant exclusion criteria (e.g., BP > 140/90).<sup>27</sup>  
 122 Therefore, we recommend that patients with low dependence, as determined by the HSI, clinical  
 123 practice guidelines, and manufacturer’s prescribing data, be started on the 14mg/day nicotine  
 124 patch while patients with moderate to high dependence be started on the 21mg/day patch as these  
 125 doses have been studied most extensively and have the strongest evidence.<sup>27</sup> Generally, most  
 126 patients can be started on the 2mg strength of the lozenge/gum. However in highly dependent  
 127 individuals, the 4mg dose can be considered to achieve nicotine concentrations closer to those  
 128 from heavy smoking.<sup>26</sup> Short-acting NRT doses are not clearly set but a good target may be  
 129 between 6-10 doses per day with tapering.<sup>21</sup> Since studies of combination or high-dose NRT  
 130 have not demonstrated significant adverse effects, this proposed dosing regimen is considered  
 131 safe to use.<sup>27</sup>

132  
 133 *Weeks 1-4: Starting Combination NRT*

134 On their quit date, patients will start with the nicotine patch and short-acting NRT. Though short-  
 135 acting NRT is typically used as needed, it may be beneficial in the initial weeks for patients to  
 136 use it routinely (e.g.  $\geq 6$  doses per day at scheduled intervals) to reduce cravings and withdrawal  
 137 symptoms.<sup>7</sup>

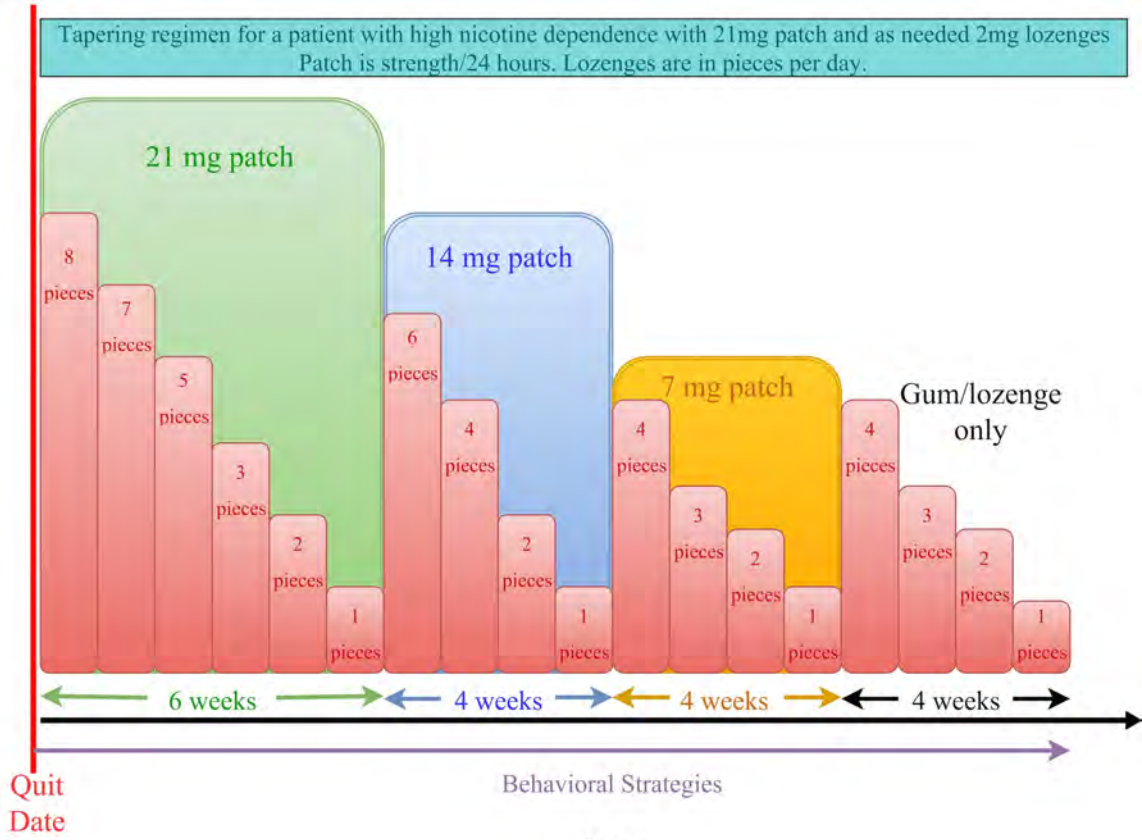


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*Tapering Combination NRT*

In general, a step-down approach can be used and NRT can be tapered over 2-4 months. However, some patients may require longer depending on their response to therapy. Though this duration is longer than recommended by the package insert, there has been some evidence demonstrating the efficacy and safety of extended treatment NRT compared to conventional treatment.<sup>27</sup> Once withdrawal symptoms have diminished, use of short-acting NRT can be tapered as needed through incorporation of behavioral strategies. For example, patients can use the strategy of substituting nicotine gum with sugar-free gum to reduce their daily use. When patients have reduced their short-acting NRT to 1-2 doses per day and feel ready, they can reduce to the next patch strength. Since there is a difference of 7mg/day of nicotine between patch strengths, patients may initially experience increased cravings. To offset this, patients may temporarily increase their short-acting NRT use as needed. Patients should be encouraged to continue utilizing behavioral strategies and to use the least amount of short-acting NRT possible to manage their cravings. Patients should continue to incorporate behavioral strategies to reduce their NRT use until they are ready to step down to the next patch. This tapering strategy should be continued until the patient is maintained solely on short-acting NRT and then tapered off of NRT completely. Figures 1-3 represent various tapering strategies for a patient with high nicotine dependence with Figure 1 illustrating the above tapering strategy. The following represent three possible tapering strategies. The duration of each step may be extended or shortened depending on the patient's progress and the tapering regimen should be individualized per patient.

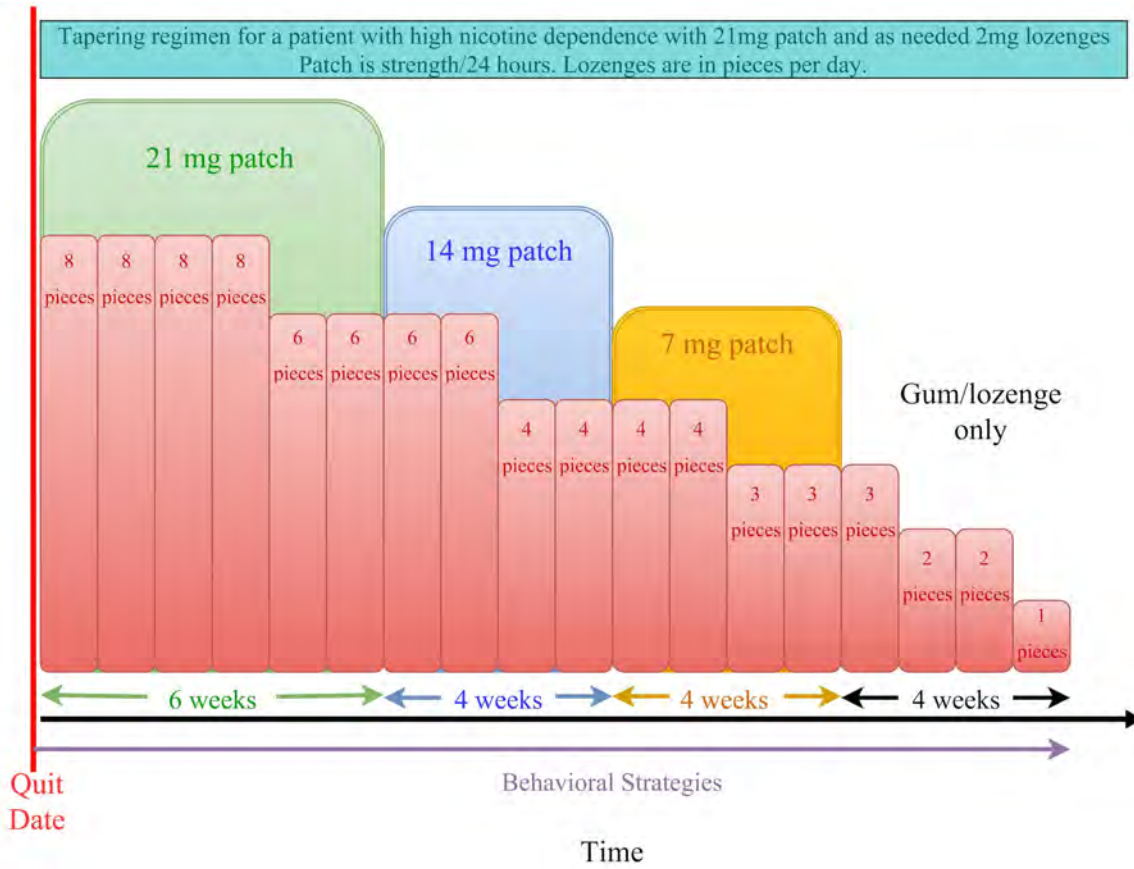
162 **Figure 1.** Sample tapering regimen. (2-column fitting image)



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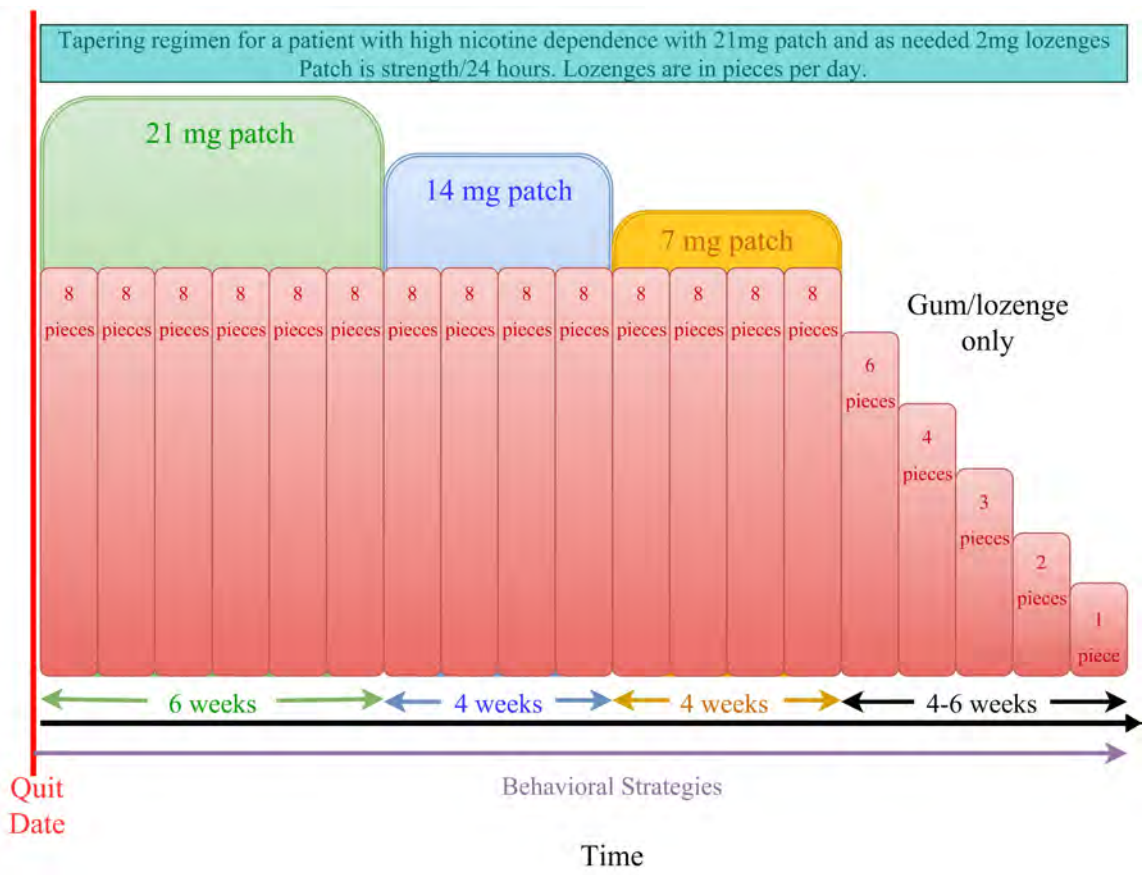
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165 **Figure 2.** Sample tapering regimen with side-by-side tapering of patch and lozenge. (2-column  
 166 fitting image)



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 168

169 **Figure 3.** Sample tapering regimen with tapering of patch and lozenge separately. (2-column  
 170 fitting image)



171  
 172

173 **Conclusion**

174 Combination NRT is a safe and effective aid for smoking cessation, but under-utilized due to  
 175 lack of guidance for dosing and titration.<sup>1-6</sup> Combination NRT is effective because it provides  
 176 relief of background and cue-induced cravings, has a lower risk for dependence, and may be  
 177 considered for all patients who wish to quit smoking.<sup>9-11</sup> Though nicotine gum, lozenge, nasal  
 178 spray, and oral inhaler have all been shown to be effective in combination NRT, each form  
 179 carries its advantages and disadvantages.<sup>6,10-11</sup> While the nasal spray and nicotine inhaler may  
 180 perpetuate physiological and behavioral dependence on nicotine, they may be preferred in  
 181 patients who cannot tolerate oral forms of nicotine. Therefore, selection of short-acting NRT  
 182 should be individualized. The initial dose of patch and short-acting NRT should be based on the  
 183 patient's tobacco dependence as assessed by the HSI.<sup>24-25</sup> A tapering, step-down approach with a  
 184 long-acting and short-acting NRT will assist in reducing nicotine dependence (Figures 1-3). The

185 tapering regimen should be individualized per patient and should be adjusted based on the  
186 patient's progress. Providers should educate patients on the incorporation of behavioral strategies  
187 with combination NRT to reduce their nicotine dependence over time.<sup>22</sup> By incorporating  
188 behavioral strategies and a step-down tapering approach, providers can effectively utilize  
189 combination NRT to help their patients to quit smoking and improve their overall health.

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