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Authors

Hsia, Stephanie L
Myers, Mark G
Chen, Timothy C

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Title page

Combination nicotine replacement therapy: dosing guidance and recommendations

Authors

Stephanie L. Hsia, PharmD[a]
Mark G. Myers, PhD[a,b]
Timothy C. Chen, PharmD[a,b]

[a]VA San Diego Healthcare System (VASDHS), 3350 La Jolla Village Drive (119), San Diego, California, USA 92161 [stephanie.hsia@va.gov] [timothy.chen@va.gov]
[b]Department of Psychiatry, University of California, San Diego, 9500 Gillman Drive, MC 0603, La Jolla, California, USA 92093. [mgmyers@ucsd.edu][tic072@ucsd.edu]

Corresponding author

Stephanie L. Hsia, PharmD
Email: stephanie.hsia@va.gov

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Abstract

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

Problem

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

Rationale and Evidence

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

Abbreviations

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

Dosing in Published Studies

Dosing strategies of combination NRT, which are summarized in Table 1, vary between studies.[6, 12-19]

Abbreviations

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

Table 1. Summary of combination NRT dosing utilized in randomized, controlled trials.[6, 12-19]

Study	Nicotine Patch Dosage	Nicotine Gum, Lozenge, Spray Dosage
Kornitzer 1995	• 15mg/16 hr x 12 weeks • 10mg /16 hr x 6 weeks • 5mg/16 hr x 6 weeks	• Gum (strength not reported) • At least 4 pieces/day x 12 weeks
Puska 1995	• 15mg/16 hrs x 12 weeks	• Gum (2mg) • At least 4 pieces/day
Blondal 1999	• 15mg x 3 months • Wean over 2 months	• Nasal spray • 0.5mg/dose x 1 year
Bohadana 2000	• 15mg/16 hr x 6 weeks	• Inhaler 4mg/cartridge • 6-12 cartridges/day x 3 months
Croghan 2003	• 15mg/16 hr x 6 weeks	• Nasal spray 0.5 mg/dose • 6 weeks • Max: 5 doses/hr, 40 doses/day
Cooney 2009	• 21mg/24 hr x 8 weeks • 14mg/24 hr x 2 weeks • 7mg/24hr x 2 weeks	• Gum (2mg) • At least 6 pieces/day x 24 weeks • Max: 20 pieces/day
Piper 2009	• 21mg/24 hr • 14mg/24 hr • 7mg/24 hr • Tapered down over 8 weeks	• Lozenge (2mg/4mg)[a] • 12 weeks
Smith 2009	• 21mg/24 hr x 4 weeks • 14mg/24 hr x 2 weeks • 7mg/24 hr x 2 weeks	• Lozenge (2mg/4mg)[a] • 1 lozenge Q1-2 hrs x 6 weeks • 1 lozenge Q2-4 hrs x 2 weeks • 1 lozenge Q4-8 hrs x 2 weeks
Schlam 2016	• 21mg/24 hr x 22 weeks if smoking > 9 cigarettes/day • 21mg/24 hr x 4 weeks if smoking 5-9 cigarettes/day • 14mg/24 hr x 2 weeks • 7mg/24 hr x 2 weeks	• Gum (2mg/4mg)[a] • 1 piece Q1-2 hrs • At least 5 pieces/day
Baker 2016	• If smoking > 10 cigarettes/day o 21mg/24 hr x 8 weeks o 14 mg/24 hr x 2 weeks o 7mg/24 hr x 2 weeks • If smoking 5-10 cigarettes/day o 14mg/24 hr x 10 weeks o 7mg/24 hr x 2 weeks	• Lozenge (2mg/4mg)[a] • At least 5 lozenges/day x 12 weeks

[a]Participants received 4mg if they smoked within 30 minutes of waking and 2mg otherwise

Dosing Recommendations, Tapering Strategies, and Behavioral Interventions

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

Behavioral Interventions

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

Selecting a Short-Acting Formulation of NRT

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

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

Dosing Recommendations

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

Table 2. Heaviness of Smoking Index (HSI) for nicotine dependence.[24- 25]

Heaviness of Smoking Index (HSI)	
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

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

Weeks 1-4: Starting Combination NRT

On their quit date, patients will start with the nicotine patch and short-acting NRT. Though short-acting NRT is typically used as needed, it may be beneficial in the initial weeks for patients to use it routinely (e.g. ≥ 6 doses per day at scheduled intervals) to reduce cravings and withdrawal symptoms.[7]

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.[27] 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.

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

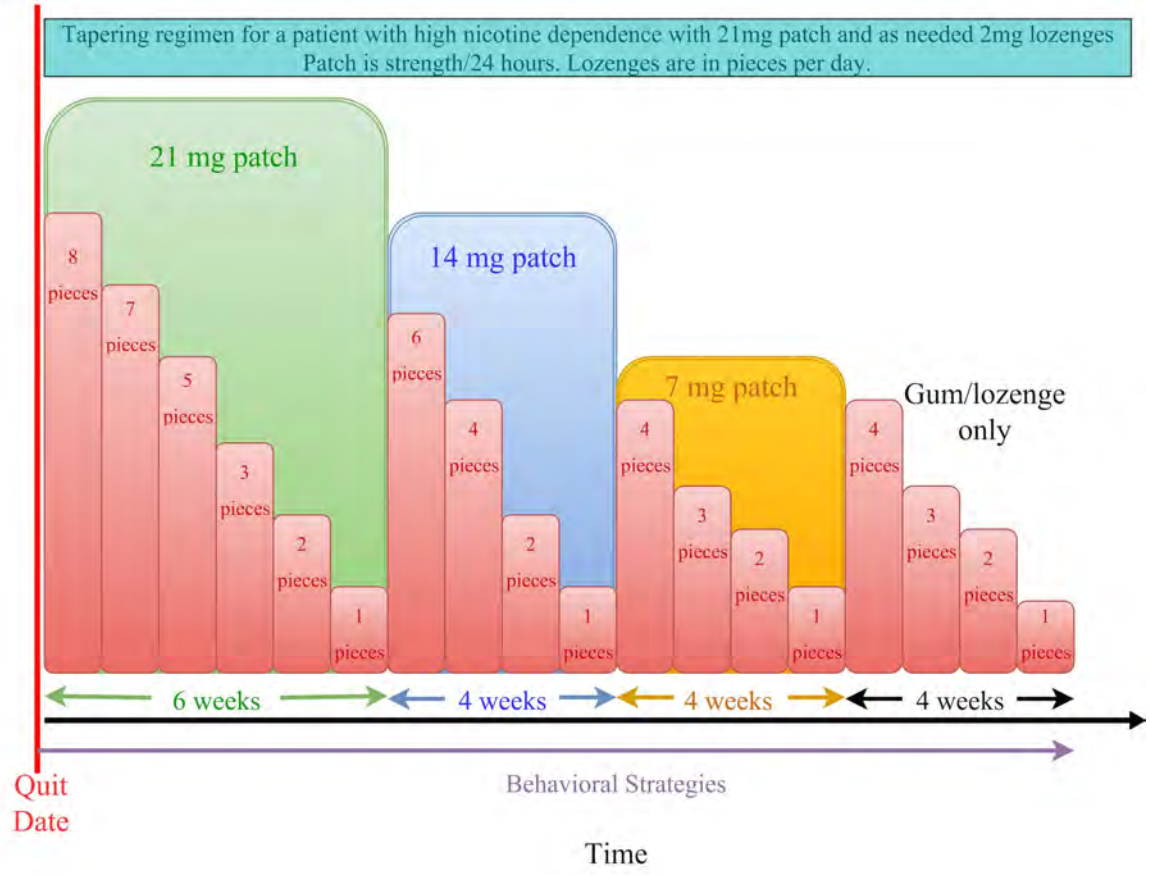


Figure 2. Sample tapering regimen with side-by-side tapering of patch and lozenge. *(2-column fitting image)*

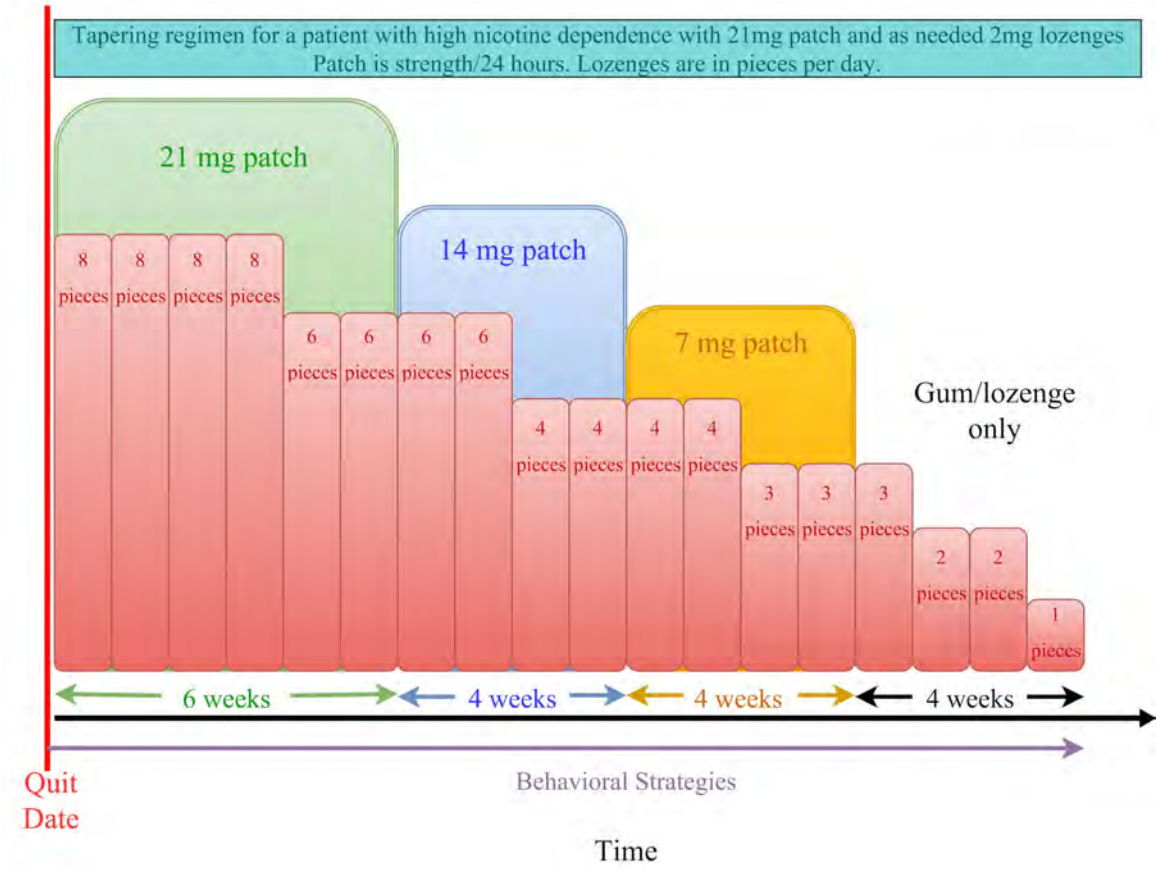
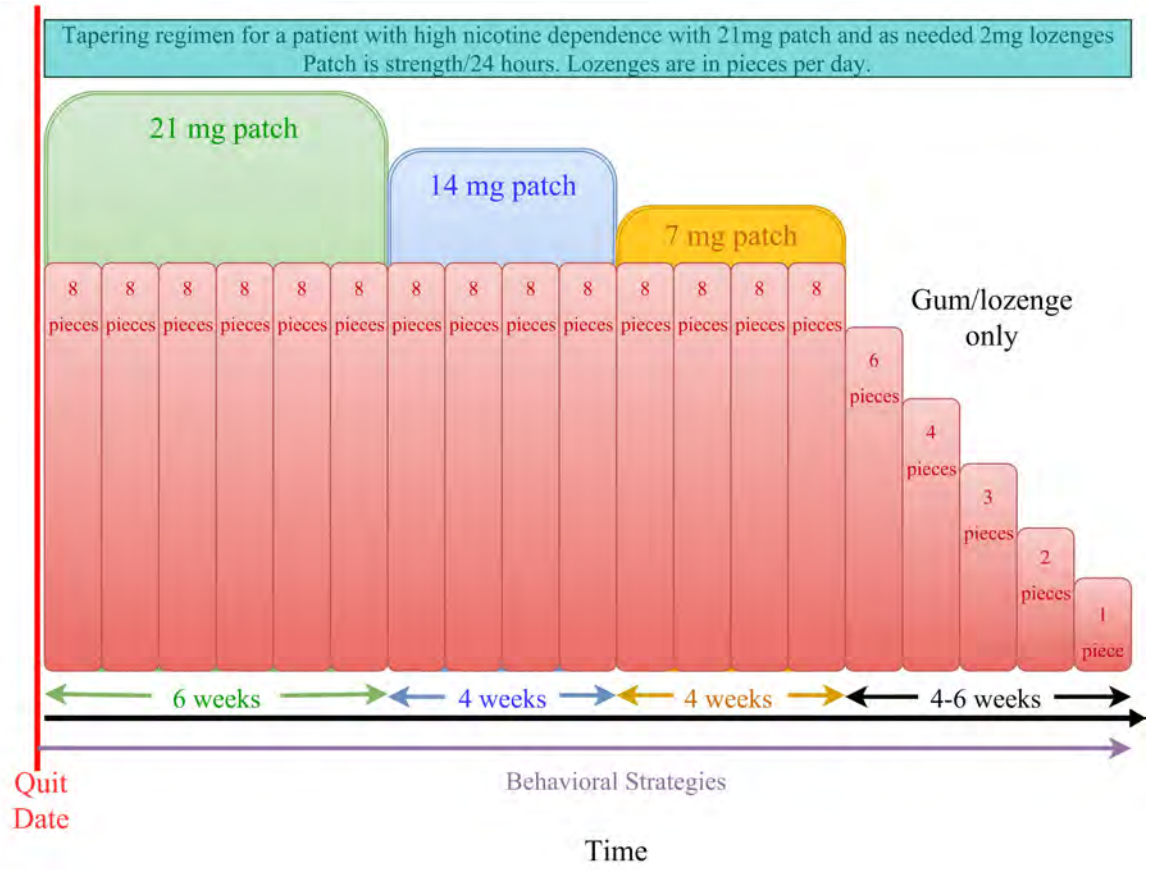


Figure 3. Sample tapering regimen with tapering of patch and lozenge separately. *(2-column fitting image)*



Conclusion

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

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

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