COMMENTARY

Addressing the Evidence for FDA Nicotine Replacement Therapy Label Changes: A Policy Statement of the Association for the Treatment of Tobacco Use and Dependence and the Society for Research on Nicotine and Tobacco

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ABSTRACT

Cigarette smoking creates a substantial public health burden. Identifying new, effective smoking cessation interventions that optimize existing interventions and promoting effective use of approved medications is a priority. When used as directed, nicotine replacement therapy (NRT) aids smoking cessation, but there is opportunity for improving its effectiveness. Until recently, NRT use guidelines advised smokers to begin using NRT on their quit date, only to use 1 NRT formulation at a time, to refrain from using NRT while smoking, and to stop NRT within 3 months regardless of progress. The Food and Drug Administration (FDA) issued a recent announcement allowing for NRT labeling changes with applications from pharmaceutical companies for such changes, and we applaud this decision. Nevertheless, additional revisions are warranted by current research. There is robust evidence that combining a longer-acting form (e.g., patch) with a shorter-acting form (e.g., lozenge) is more effective than NRT monotherapy and is safe. Moreover, extant evidence suggests that NRT use prior to a quit attempt or for smoking reduction as part of a quit attempt is safe and as effective as starting NRT on quit date. Specifically, prequit nicotine patch increases quit rates and may engage additional recalcitrant smokers. Last, NRT use longer than 3 months is safe and may be beneficial for relapse prevention in some smokers. This report summarizes the FDA announcement, reviews the evidence for further revisions to current FDA NRT guidelines, and makes recommendations for over-the-counter (OTC) NRT labeling to allow for (1) combined use of faster-acting NRT medications with nicotine patch, (2) nicotine patch use prior to quit date or NRT for smoking reduction as part of a quit attempt, and (3) prolonged NRT for up to 6 months without healthcare provider consultation.

INTRODUCTION

An estimated 18% of American adults smoke cigarettes (Centers for Disease Control and Prevention, 2014), which is the leading preventable cause of morbidity and mortality in the United States (US) and many other parts of the world (Mokdad, Marks, Stroup, & Gerberding, 2004; U.S. Department of Health and Human Services, 2014). Smoking causes cardiovascular disease, many cancers, respiratory illnesses such as chronic obstructive pulmonary disease (COPD), and contributes to more than 480,000 deaths per year (Mokdad et al., 2004; U.S. Department of Health and Human Services, 2014). Thus, smoking abstinence is crucial for reducing the risk for harm: cessation has substantial health benefits at all ages (Anthonisen et al., 2005; Gellert, Schottker, & Brenner, 2012). Clearly, smokers need to have available to them all effective methods of quitting.

Nicotine replacement therapy (NRT) is a safe and efficacious smoking cessation aid that is widely available to smokers. Further, the over-the-counter (OTC) status of many NRT products (gum, lozenge, and patch) increases access and utilization (Burton, Gitchell, & Shiffman, 2000; Shiffman et al., 1997). Nevertheless, the current labeling of NRT may undermine its positive public health impact. Smokers are advised to start NRT only when they stop smoking (i.e., on

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their "quit date"), to only use one NRT product at a time, to refrain from using NRT if they resume smoking, and to stop NRT within 3 months, regardless of their progress (Stapleton, 2008). This creates the impression that NRT is only safe and/or effective when used under these conditions; however research evidence conflicts with this notion. Further, these use guidelines suggest that there is an optimal way for all smokers to quit smoking despite limited empirical support. These restrictions may deter some smokers from using NRT for a quit attempt and/or may limit the benefits smokers can derive from their use.

The Food and Drug Administration has recently issued a public announcement that they will allow modification of 3 aspects of NRT labeling: (1) deleting the warning not to use NRT if smokers continue to smoke, chew tobacco, or use [a different NRT product] or other nicotine containing products, (2) revising the recommendation that smokers should stop smoking completely before beginning NRT to now state that smokers should begin using NRT on their quit day, and (3) revising the recommendations for NRT duration to allow for a longer period of NRT use following treatment completion but only under the consultation of a health care provider (Food and Drug Administration, 2013a, 2013b). These statements are a step in the right direction and permit more flexible use of NRT, including several empirically supported modifications of NRT regimens. There is a need, however, for additional NRT labeling modifications based on the evidence presented in this illustrative review.

Combining a long-acting form of NRT (e.g., nicotine patch) with a faster-acting formulation (e.g., nicotine gum), often referred to as "dual NRT" or "combination NRT," is a highly efficacious and safe smoking cessation treatment (Kornitzer, Boutsen, Dramaix, Thijs, & Gustavsson, 1995; Piper et al., 2009; Stead et al., 2012). Likewise, use of NRT prior to the quit date or for smoking reduction as part of a quit attempt is safe, and in the case of nicotine patch, may increase smoking abstinence (Rose, Herskovic, Behm, & Westman, 2009; Schuurmans, Diacon, van Biljon, & Bolliger, 2004; Stead et al., 2012) and extended NRT use is safe and may be an effective relapse prevention intervention for some smokers (Agboola, McNeill, Coleman, & Leonardi Bee, 2010; Joseph et al., 2011; Schnoll et al., 2010). Further, these flexible treatment strategies may have advantages for smokers who prefer quitting by smoking reduction or whom could benefit from a longer course of treatment. Therefore, explicit statements should be added to FDA labels for NRT stating that: (a) use of longer-acting NRT concomitantly with faster-acting NRT is safe and likely improves quit rates among smokers who smoke ≥10 cigarettes/day; (b) prequit NRT use (i.e., either for nicotine preloading or gradual reduction as part of a quit attempt) is safe, as effective as starting NRT on quit date, and in the case of prequit nicotine patch may increase quit rates, and (c) extended use of NRT duration up to 6 months is safe and may be beneficial for relapse prevention among smokers who do not feel confident in their ability to maintain abstinence as they near the end of the standard 3-month duration. Importantly, allowing more flexible approaches to quitting, including prequit use of NRT, and use of NRT for reduction prior to a quit attempt may engage additional smokers who do not feel ready to attempt abrupt cessation in evidence-based methods of quitting.

EVIDENCE SUMMARY

Use of Long-Acting NRT Concomitantly With Short-Acting NRT Is Safe and Increases Smoking Abstinence

There are 5 FDA-approved NRT formulations for smoking cessation: (1) nicotine patch, (2), nicotine gum, (3) nicotine lozenge, (4) nicotine nasal spray, and (5) nicotine inhaler. Nicotine patch, gum, and lozenge are available OTC in the United States; nicotine nasal spray and inhaler are available only by prescription. The nicotine patch is a longer-acting product that can deliver nicotine continuously for up to 24 hr whereas the oral/nasal products are shorter-acting (i.e., up to 1–2 hr per dose) acute doses. Smokers are currently advised to only use 1 of these products when making a quit attempt because the FDA has not explicitly approved the combined use of NRT products. Consequently, combination NRT cannot be marketed for use as dual therapy or sold together in 1 package. Moreover, many clinicians and most smokers are unaware that dual therapy is safe and effective, given that it is not a FDA approved medication regimen.

There is substantial evidence that combining a nicotine patch with a shorter-acting NRT formulation is safe and yields better smoking cessation outcomes than NRT monotherapy (Stead et al., 2012). The U.S. Department of Health and Human Services Clinical Practice Guideline for Tobacco Use and Dependence meta-analysis designated combination NRT as the most effective treatment option (Fiore et al., 2008). In a randomized clinical trial (RCT) of 300 smokers, nicotine gum + nicotine patch therapy resulted in significantly higher 3-month quit rates (39.3%) than nicotine gum + placebo patch (28%) (Puska et al., 1995). A similar RCT of 374 smokers showed combination therapy (nicotine patch + nicotine gum) was superior to monotherapy (nicotine patch + placebo gum) in significantly delaying relapse and increasing 6-month abstinence rates (27.5% vs. 15.3%) (Kornitzer et al., 1995). Another investigation found that nicotine patch + nicotine gum significantly delayed smoking relapse and was associated with significantly higher 12-month smoking quit rates relative to monotherapy (nicotine patch + placebo gum) (13% vs. 0%) in 96 smokers receiving treatment for alcohol problems (Cooney et al., 2009).

Similar results have been observed with other combinations of NRT. For instance, in a RCT of 1,384 smokers, combined nicotine nasal spray + nicotine patch was associated with significantly higher quit rates at 6 weeks (27.1%) than either nicotine nasal spray (13.6%) or nicotine patch alone (21.1%) (Croghan et al., 2003). Combining nicotine patch with nicotine inhaler therapy significantly increased 3-month quit rates and delayed relapse compared to nicotine inhaler monotherapy (Bohadana, Nilsson, Rasmussen, & Martinet, 2000). Analysis of a large-scale RCT of 5 smoking cessation pharmacotherapies (i.e., nicotine patch, nicotine lozenge, bupropion, nicotine patch + nicotine lozenge, bupropion + lozenge) using placebo head-to-head comparisons (N = 1,504) showed that nicotine patch + nicotine lozenge significantly increased 6-month quit rates (40.1% for nicotine patch + nicotine lozenge vs. 22.2% for placebo) (Piper et al., 2009).

All studies tested combination NRT among smokers who reported smoking ≥10 cigarettes per day. Adverse effects were minimal and combination NRT was well tolerated and there were few differences in adverse effects between dual NRT and NRT monotherapy.

Combination NRT may enhance smoking cessation success through its effects on nicotine withdrawal and/or smoking cravings. In accordance with this premise, a study compared the effectiveness of nicotine patch and nicotine gum alone or in combination for attenuating nicotine withdrawal symptoms (N = 28) using a within-subjects design in which all participants served as their own controls (Fagerström, Schneider, & Lunell, 1993). Participants rated their withdrawal for 3 days in each of 4 conditions: (1) nicotine gum + nicotine patch, (2) nicotine gum + placebo patch, (3) placebo gum + nicotine patch, and (4) placebo gum + placebo patch. Combination NRT provided the greatest nicotine withdrawal relief among all the conditions and was the only treatment that reduced withdrawal symptoms to baseline levels. A recent secondary analysis of the large scale RCT of 5 smoking cessation pharmacotherapies (Piper et al., 2009), demonstrated that greater suppression of smoking craving was the mechanism by which combination therapy resulted in significantly higher quit rates than monotherapy (Bolt, Piper, Theobald, & Baker, 2012). It has also been suggested, though not proven, that the addition of acute NRT to nicotine patch treatment may afford smokers a tool for reacting to acute episodes of craving that may arise even on patch treatment, and which are associated with smoking lapses (Ferguson & Shiffman, 2009). Further, the benefits of combination NRT are unlikely to simply reflect a higher nicotine dose, since high-dose patches have modest incremental efficacy (Stead et al., 2012), while adding acute NRT medicines to patch results in significant gains in efficacy with only modest increases in nicotine dose.

Taken together, these studies show that use of longer-acting NRT concomitantly with faster-acting NRT is a safe, well-tolerated treatment strategy that increases smoking quit rates. Combination NRT may also provide a more potent treatment that better alleviates nicotine withdrawal and cravings than NRT monotherapy. NRT labeling should specifically state that combination NRT is safe in general and more effective than NRT monotherapy for smokers who smoke ≥10 cigarettes per day.

Starting Use of NRT While Smoking Is Safe, as Effective as NRT Use Starting on Quit Date, and May Promote Subsequent Abstinence

Prescheduled Quit Date NRT Use

The revised FDA NRT use guidelines recommend that smokers only begin NRT on the day of their quit date based on the assumption that concomitant use of NRT and smoking will lead to nicotine toxicity. In fact, use of NRT while still smoking is well tolerated and safe, and prequit nicotine patch use can increase the odds of quitting. Therefore, smokers should be advised that they can use NRT to preload before making an abrupt quit attempt.

Prior research has demonstrated that starting nicotine patch prior to cessation increases quit rates relative to starting patch at the time cessation is initiated. In one study of 400 smokers, 2 weeks of precessation nicotine patch (followed by 10 weeks of nicotine patch starting on the quit date) significantly doubled end of treatment continuous abstinence rates compared to 2 weeks of precessation placebo patch (Rose et al., 2009). A similar study with 200 smokers found that sustained abstinence rates up to 6 months were significantly higher among those who received precessation nicotine patch therapy versus precessation placebo patch (22% vs. 12%) and the advantage of precessation nicotine patch therapy was higher for heavier smokers (Schuurmans et al., 2004). Although there are some negative findings (Bullen et al., 2010; Etter, Huguelet, Perneger, & Cornuz, 2009; Hughes, Solomon, Livingston, Callas, & Peters, 2010), most of these studies tested precessation NRT other than nicotine patch. Furthermore, the overall conclusion from meta-analyses is that use of NRT prior to a quit attempt is safe, at least as effective as starting NRT on quit date, and when prequit nicotine patch trials are pooled together, may actually increase quit rates (Stead et al., 2012). Therefore, NRT labeling should permit use of precessation NRT for nicotine preloading prior to quitting.

Use of NRT for Smoking Reduction as Part of a Quit Attempt

In addition to nicotine preloading, prequit NRT use may have other advantages for some smokers. Not all smokers prefer and can sustain abrupt smoking cessation. In fact, a substantial percentage of smokers prefer to reduce smoking prior to total abstinence (Shiffman et al., 2007). Meta-analysis indicates that NRT for gradual reduction is effective for achieving smoking abstinence among smokers either unwilling or unable to attempt abrupt cessation (Wang et al., 2008) and that abrupt cessation and "reduce to quit" models yield comparable quit rates (Lindson, Aveyard, & Hughes, 2010). For example, a RCT was conducted comparing nicotine vs. placebo gum for up to 8 weeks while still smoking in a sample of 3,297 smokers interested in quitting by gradual reduction (Shiffman, Ferguson, & Strahs, 2009). Smokers used nicotine gum (or placebo) to facilitate reduction, as a method of quitting. Upon achieving 24-hr abstinence, smokers were instructed to use gum in accordance with OTC directions for cessation. Participants who did not achieve 24-hr abstinence were counted as treatment failures in subsequent analyses. Smokers who received nicotine gum were significantly more likely to achieve a ≥50% reduction in smoking after 2 weeks of treatment than smokers who received placebo gum. Moreover, smokers who reduced their smoking by ≥50% had significantly higher quit rates than smokers who were unable to achieve this criterion. Overall, smokers who were treated with active gum achieved higher abstinence rates than those on placebo. These results are consistent with other RCTs of smokers willing to reduce their smoking, even if they were not ready to quit immediately. These studies demonstrated that nicotine gum, inhaler, and patch therapy used in this manner significantly increased long-term quit rates (i.e., at ≥6 months) compared to placebo (Carpenter, Hughes, Solomon, & Callas, 2004; Chan et al., 2011; Kralikova, Kozak, Rasmussen, Gustavsson, & Le Houezec, 2009; Wang et al., 2008).

Smokers who do not respond to repeated abrupt cessation advice might find a "reduce to quit" strategy with NRT more appealing (Hughes & Carpenter, 2006), and NRT labeling should specifically allow for NRT use in this manner. Further, smokers could be advised that NRT promotes smoking cessation through different pathways: by facilitating reductions in smoking to achieve total abstinence and by helping maintain abstinence once a quit attempt has been initiated (i.e., in line with current use guidelines) (Hughes & Carpenter, 2006).

Extended Duration NRT Is Safe, as Effective as Short-Term NRT, and May Be an Effective Relapse Prevention Intervention for Some Smokers

When nicotine gum was available only by prescription it was approved for 6 months of use and labeling directed users to

carry gum with them even after 6 months in case they needed it to cope with cravings to smoke. At present, NRT is only approved for short-term use to assist with smoking cessation. For example, smokers are advised to stop nicotine patch therapy within 3 months. The new use guidelines allow for longer use only under the consultation of a health care provider. The risk of relapsing is greatest during the first year of quitting smoking (McWhorter, Boyd, & Mattson, 1990). An estimated 50–60% of smokers will relapse within a year of quitting (Tonstad et al., 2006) and only 3–5% are still abstinent at 1 year (Hughes, Keely, & Naud, 2004). Thus, more effective relapse prevention interventions are needed for smoking.

A number of prior studies suggest that short- and long-term courses of NRT have equivalent efficacy (Stead et al., 2012). Recent research evidence, however, suggests that extended duration NRT may increase quit rates and recovery from smoking lapses. An investigation was conducted with 568 smokers who were randomly assigned to receive either 24 weeks of nicotine patch or 8 weeks of nicotine patch + 16 weeks of placebo patch (Schnoll et al., 2010). Smokers in the extended nicotine patch group had significantly higher 24-week quit rates (31.6%) and a significantly slower latency to relapse than smokers in the standard nicotine patch group (14.5%), though this effect was no longer statistically significant at 52-weeks. Another RCT compared evidence-based smoking cessation treatment with telephone-based chronic disease management (Joseph et al., 2011). All smokers ($N = 443$) received five telephone counseling calls and NRT by mail for 4 weeks. They were then randomized to either: (1) usual care (two additional counseling calls) or (2) longitudinal care (NRT and continued counseling for an additional 48 weeks). Longitudinal care revealed significantly higher 6-month continuous abstinence rates than usual care (30.2% vs. 23.5%). Further, longitudinal care was associated with a greater increase in the cumulative frequency of quitters over the 12-month treatment period than usual care. In both studies, extended NRT use was well tolerated. These findings are consistent with a systematic review of smoking relapse prevention strategies that demonstrated use of NRT for up to 9 months is beneficial for preventing relapse (Agboola et al., 2010).

A subset of smokers who successfully quit engage in extended use of NRT beyond the recommended timeframe, on their own (Murray et al., 1996), and such prolonged use is associated with improved abstinence rates. In a RCT of nicotine gum (conducted at a time when gum was only available by prescription and indicated for ≥6 months), smokers ($N = 315$) received either nicotine or placebo gum and advice to stop use after 4 months along with specific instructions for how to taper use (Hughes et al., 1991). Gum was available, however, to all participants for 12 months. Among quitters, 46% of smokers in the nicotine group reported gum use beyond 4 months compared to 17% of smokers in the placebo group ($p = .02$). Another study investigated the occurrence of long-term nicotine gum use in smokers receiving nicotine gum through a comprehensive smoking cessation clinic ($N = 538$) (Hajek, Jackson, & Belcher, 1988). Smokers were advised to stop nicotine gum use after 3 months, but gum continued to be available after that time. At 1-year follow-up, 6% of smokers still reported use of nicotine gum, representing 25% of lapse-free abstainers. Long-term gum users in this study were heavier, more dependent smokers who used more gum from the very first day of treatment. Analyses of OTC NRT use in real-world environments estimates that the proportion of smokers who use NRT for 6 months or more is about 6% (Shiffman, Hughes, Di Marino, & Sweeney, 2003; Shiffman, Hughes, Pillitteri, & Burton, 2003). Two thirds of those using nicotine gum for 6 months were abstinent, and two thirds of those using the gum at 6 months were doing so in order to maintain abstinence (Shiffman et al., 2003).

The meta-analysis conducted by Fiore et al. (2008) for the last update to the Tobacco Clinical Practice Guideline concluded that long-term nicotine patch and nicotine gum may be more effective for some smokers and advised that it may be appropriate for these smokers to use treatment for longer periods than currently recommended by NRT use guidelines. In addition, the results of the meta-analysis indicated that long-term nicotine patch plus ad libitum NRT had the largest effects on quit rates. Thus, extended duration NRT, while not common, is safe (Murray et al., 1996), as effective as short-term NRT, and may increase quit rates among smokers who do not feel confident in their ability to maintain abstinence as they near the end of the standard 3-month NRT duration. NRT labeling should permit such smokers to continue without requiring consultation from a healthcare provider.

CONCLUSIONS

NRT is an effective, widely available smoking cessation aid. Although the FDA, in response to several petitions, announced that they will allow some label changes for NRT, additional changes are necessary to be consistent with extant scientific evidence. The findings outlined in this report emphasize the critical importance of revising NRT labels. The FDA's proposal to revise parts of the NRT warnings labels is a step in the right direction, but we recommend more explicit statements regarding the different conditions in which NRT is safe and effective, in line with current research evidence.

RECOMMENDATIONS

Based on the evidence presented in this policy statement, we recommend that the FDA issue a public notice that allows pharmaceutical companies to apply to revise current label guidelines regarding the use of NRT concomitantly with other NRT, precessation use of NRT and use of NRT for reduction as part of a quit attempt, and the duration of NRT.

We specifically recommend that the FDA allow companies to make the following changes in label directions, to enable more smokers to successfully quit smoking in the United States:

1. Allow combined use of acute oral nicotine medications (gum and lozenge) with nicotine patches, informing consumers of the potential for incremental efficacy.
2. Allow use of nicotine patch prior to a target quit date as a nicotine preloading strategy and for smoking reduction as part of a quit attempt.
3. Allow extended use of NRT for up to 6 months without consultation with a healthcare provider for smokers who feel they need longer treatment for relapse prevention.

DECLARATION OF INTERESTS

SRNT takes great care to avoid any potential or actual conflicts of interest that may emanate from a personal, professional,

or business interest of a member of the Writing Committee. Conflict of interest statements from the Writing Committee were obtained and are on file with the association. The following financial relationships were disclosed: Lisa Fucito, Matthew Bars, Ariadna Forray, Alana Rojewski—none; Saul Shiffman–consulting to GlaxoSmithKline (GSK), which makes NRT medications, and membership in JSR, which is developing NRT medications; Peter Selby—unrestricted grants and consultation to Pfizer Canada (does not market NRT in Canada), reduced price NRT for clinical trials based on open tender from Johnson and Johnson and Norvatis (makers of NRT in Canada); Robert West—consulting for Pfizer, Johnson and Johnson, McNeil, GSK, Nabi, Novartis, and Sanofi-Aventis, has a share of a patent for a novel nicotine delivery device, and is a trustee of QUIT, a charity that provides stop smoking support; Jonathan Foulds—consulting for a number of pharmaceutical companies producing smoking cessation products, including GSK, Novartis, Pfizer, Johnson and Johnson, and Cypress Bioscience; Benjamin Toll—commercial research grants and support in excess of $10,000 from Pfizer for medicine only.

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