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Cautions and warnings on the US OTC label for nicotine replacement: What's a doctor to do?

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ABSTRACT

Background: FDA-approved labeling for over-the-counter (OTC) nicotine replacement therapy (NRT) limits duration of use to a relatively short period of time (10–12 weeks) and explicitly advises against NRT use while smoking or with additional forms of NRT.
Objective: To consider and summarize evidence accumulated since the OTC label was created regarding the safety and efficacy of longer-term and concomitant use to provide recommendations regarding these uses.
Method: Literature searches were conducted on Medline, journal websites, and Internet search engines, with findings reviewed by six smoking cessation researchers.
Results: Persistent (i.e., long-term) use of NRT does not appear harmful and self-selected persistent use is primarily driven by concerns about relapse to smoking, not addiction. Similarly, continued use of NRT and tobacco during a lapse or relapse and combination NRT treatment do not appear harmful and appear to enhance efficacy.
Conclusions: Persistent users of NRT should be counseled to reduce and stop NRT only when they are not concerned about relapsing to smoking. Use of NRT with return to smoking during a lapse or relapse should not be automatically discontinued. Combination NRT therapy should be considered for all smokers, especially those who are unable to quit smoking using a single form of NRT.

1. Background

Nicotine replacement therapy (NRT) is a first-line recommendation for treating tobacco dependence, having been shown to increase cessation rates by 1.5 to 2 times across a wide range of populations and settings (Stead, Perera, Bullen, Mant, & Lancaster, 2008; Fiore, Jaen, Baker et al., 2008; NICE, 2002; WHO/Europe, 2000; West, McNeill, & Raw, 2000). Most NRT products have been available over-the-counter (OTC) without a prescription in the US since 1996. In the OTC setting, FDA-approved product labeling is the primary tool for guiding safe and effective use of the medication by smokers. In several instances, the label warns against certain uses, and directs the user to consult a doctor for guidance. In this paper, we summarize the evidence relating to three of the issues cited in the OTC NRT label and provide recommendations for clinicians for how best to advise patients regarding these issues: duration of use, concurrent use of NRT with smoking, and combination therapy with more than one form of NRT. We especially focus on the evidence that has accrued since decisions on labeling were made.

1.1. Duration of use

The OTC NRT label advises users to "stop using the nicotine gum [lozenge] at the end of 12 weeks," "stop using the patch at the end of 10 weeks," and to talk to a doctor if they believe they need to use these medications for longer. Previously, when nicotine gum was available by prescription only, patients were instructed to use the medication for 6 months. The shorter treatment duration for OTC was probably due to concerns about the abuse and dependence potential (McNeill, Foulds, & Bates, 2001). It has been suggested that prolonged use of NRT might be necessary for some smokers to maintain abstinence from cigarettes (Fiore et al., 2008) and forcing abstinence from NRT could cause some to return to smoking (Kozlowski et al., 2007).

1.2. Concurrent smoking

Current labeling for NRT products explicitly advises against smoking while using NRT; users are instructed to stop smoking completely upon initiation of medication use and discontinue

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medication use if they smoke. This restriction likely grew out of the concern that concurrent use might expose users to increased levels of nicotine. However, many smokers trying to quit do, in fact, engage in concurrent smoking and NRT use either soon after trying to quit or in the transition to a relapse (Shiffman, Hughes, Di Marino, & Sweeney, 2003). Even among successful quitters, "slips" of smoking a few cigarettes are quite common (Borland, 1990). Once a slip occurs, a strict interpretation of the label would require that the user discontinue NRT use, perhaps causing smokers to abandon their quit attempt and resume regular smoking. Emerging evidence, however, suggests that continuing use of NRT during and after such slips substantially increases the likelihood of a return to abstinence (Shiffman, Ferguson, & Gwaltney, 2006) and rarely causes significant adverse events (Fagerström & Hughes, 2002).

1.3. Combining NRT forms

Product labeling warns against use of more than one form of NRT at the same time, presumably to limit total nicotine exposure. However, research over the last two decades indicate combination therapies, particularly approaches that combine the continuous delivery of nicotine from patches with a rapid release form of NRT such as nicotine gum or lozenge, which can be taken when the smoker faces a particularly strong craving (Sweeney, Fant, Fagerström, McGovern, & Henningfield, 2001), are more effective than monotherapies and widely recommended by clinicians and national guidelines (Fiore et al., 2008).

Evaluation of the appropriateness of NRT use in each of these three circumstances should distinguish the harms due to smoking from harms attributable to nicotine. Overwhelmingly, the harmful effects from tobacco use arise not from nicotine, but from the tar and toxic gases found in tobacco smoke that are not present in NRT (USDHHS, 1990). Although it has been suggested that nicotine itself may play some role in cardiovascular disease, cancer, and perinatal morbidity, evidence in humans is limited, and the magnitude of harm from nicotine, if any, is very small (Molyneux, 2004; Benowitz, 1998; Royal College of Physicians (RCP), 2007).

While the label for NRT has remained virtually unchanged for the past 14 years, new data are available on the safety of NRT under the conditions proscribed by the OTC label. The purpose of this paper is to summarize the available evidence and provide recommendations to clinicians for how best to advise patients regarding persistent use, use of NRT upon a lapse or relapse, and combined use of NRT products. We do not review all of the relevant publications in detail, but rather summarize the most relevant clinical evidence on each issue. Although these issues have been briefly discussed in authoritative national guidelines (Fiore et al., 2008) and review articles (Kozlowski et al., 2007), the current paper provides a more thorough analysis of the relevant literature. The paper focuses on the three NRT products that are available OTC in the US: gum, patch, and lozenge.

2. Findings and recommendations

2.1. Persistent use

Each type of NRT has a recommended duration of use: 12 weeks for nicotine gum and lozenge and 10 weeks for nicotine patch. Smokers using nonprescription NRT for longer than the labeled period are advised "If you still need to use [product], talk to your doctor."

2.1.1. Prevalence and nature of persistent use

When available only by prescription, nicotine gum was indicated for 6 months of use; this was reduced to 12 weeks during the switch to nonprescription status. Under prescription use, an estimated 8–11% of nicotine gum users exceeded the recommended 6 months of use (Hughes, 1991; Johnson, Stevens, Hollis, & Woodson, 1992). Available data suggest that persistent use of NRT in the OTC setting has remained low despite the removal of prescriber control and the reduction in the recommended duration of use: two studies of OTC nicotine gum use, using different methodologies, estimated persistent use of 6 months or more at 6% (Shiffman, Hughes, Di Marino, & Sweeney, 2003; Shiffman, Hughes, Pillitteri, & Burton, 2003).

When use of NRT beyond the duration limits specified in product labeling does occur, it typically does not appear to be due to dependence on nicotine products, as defined by the Diagnostic and Statistical Manual of Mental Disorders (APA, 2000), but rather prolonged use typically represents an attempt to maintain or establish abstinence. For example, one study estimated that fewer than 2% of smokers who engaged in persistent OTC gum use (at least 3 months) meet standard criteria for drug dependence on the gum (Hughes, Pillitteri, Callas, Callahan, & Kenny, 2004). Consistent with that, most long-term users are able to stop such use without relapse to nicotine gum use or to smoking by brief tapering with nicotine gum or abrupt cessation (Hurt et al., 1995). Moreover, when individuals engaged in persistent use were asked, the majority (67%) stated they were doing so to maintain abstinence and avoid relapsing to smoking (Shiffman, Hughes, Di Marino, & Sweeney, 2003).

In fact, under-utilization of NRT is far more common than persistent use (West et al., 2000). Even smokers who do use NRT tend to use too little (particularly gum and lozenge) (Shiffman, Hughes, Di Marino, & Sweeney, 2003) and use it too briefly (Shiffman, Hughes, Pillitteri, & Burton, 2003). Guidelines for the use of nicotine gum to treat tobacco dependence, in fact, encourage sufficient use, stating that chewing gum on a fixed schedule (i.e., at least one piece every 1–2 hours for at least one to 3 months) is likely to be more beneficial than ad libitum use (Fiore et al., 2008).

2.1.2. Safety of persistent use

Available data suggest that persistent use carries few health risks (Benowitz, 1998), even among those with cardiovascular conditions (Benowitz & Gourlay, 1997; Joseph et al., 1996; Mahmarian et al., 1997) and even when used for periods of years by smokers with compromised health (Murray et al., 1996). For example, the Lung Health Study (Murray et al., 1996), a large-scale study of people with chronic obstructive pulmonary disease, encouraged smokers to use nicotine gum for smoking cessation over the 5-year study period with gum provided free of charge. This study represents the largest known experimental cohort of persistent NRT users with 1,042 (31%) intervention subjects still using the gum after 1 year. Among ex-smokers, users of nicotine gum showed no indication of harm and, in fact, had lower hospitalization rates for cardiovascular conditions compared to those who did not use the gum. Even among those who used NRT and continued to smoke, there was no indication of harm. No serious adverse events were observed as a result of long-term use of nicotine gum.

2.1.3. Efficacy of persistent use

As noted, smokers typically engage in persistent use as a means of preventing relapse, and thus enhancing efficacy. Meta analyses have generally failed to identify an overall benefit for treatment for longer than 14 weeks (Fiore et al., 2008; Stead et al., 2008). However, several individual studies have suggested benefit. One cohort study that evaluated abstinence rates among smokers treated in a tobacco dependence clinic demonstrated that smokers who used nicotine medications for longer periods of time had higher abstinence rates (Steinberg, Foulds, Richardson, Burke, & Shah, 2006). An unpublished clinical trial that examined the efficacy of extended (52 weeks) versus brief (12 weeks) nicotine gum treatment in smokers found significantly higher abstinence rates with the extended treatment compared to the brief treatment (Humfleet et al., 2001). Similarly, a double-blind, placebo-controlled trial demonstrated significantly higher abstinence rates following 24 weeks of treatment with 21 mg nicotine patch