Use of Nicotine Mouth Sprays for Tobacco Cessation: A Review

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Smoking is a taboo, and a smoker fails in quitting despite repeated attempts as tobacco in all forms contain a highly addictive chemical nicotine making it difficult for habituated tobacco users to quit. Its addictive potential is considered to be even more than cocaine or heroin. It is due to the dependency caused by the nicotine that smokers become dependent and cause severe withdrawal symptoms. Hence, nicotine replacement therapy came into play to aid in tobacco cessation. There are currently various nicotine replacement therapies, which are available currently for tobacco abstinence. In this article, we shall discuss nicotine nasal spray, mouth spray, and the nicotine inhaler.

Keywords: Cessation, Smokers, Tobacco

INTRODUCTION

Cigarette smoking habit is a chronic relapsing condition that for many users proves to be a struggle to achieve long-term abstinence that extends over years or decades. Successful therapies need to tackle the interrelated constellation of factors – Personal, family, socioeconomic, and pharmacological — so that their regular use can act as major barrier to cessation.

NICOTINE MOUTH SPRAY

There is some evidence that nicotine replacement therapies (NRT) formulations that act faster in preventing cravings for cigarettes are overall more effective in controlling withdrawal discomfort also.1,2 These medications may be useful in alleviating intermittent urges to smoke when a fast reduction in craving is deemed important in order to prevent relapse to smoking. Presently available oral NRT formulations provide relatively slow relief from cravings. Nicotine nasal spray (NNS) however has more immediate effects,3 but it initially causes unpleasant local irritation. The nasal spray is also a prescription-only medication in a number of countries. Delivering the nicotine via a mouth spray is one promising approach to a faster and more palatable form of nicotine delivery. Compared with chewing gum, lozenge or sublingual tablet, mouth spray delivers nicotine in the solution quickly on to a large surface area of the buccal mucosa. Pharmacokinetic studies have shown that nicotine mouth spray provides blood nicotine levels comparable to that of other NRT formulations of the same strength,4 but that the mouth spray provides maximum plasma concentrations in approximately 10 min, this is significantly faster than the other oral NRT formats.4 Long-term efficacy of nicotine mouth spray, in terms of smoking abstinence, has been demonstrated in a placebo-controlled study (sustained abstinence rates 15.7% vs. 68% at 24 weeks).5 One appreciable explanation for the faster relief from the temptation to smoke with the mouth spray is due to the speed of nicotine absorption. Earlier findings have shown that the mouth sprays increases the blood nicotine faster than the lozenges.4

If speed of nicotine absorption is the key factor that underpins these differences, we can reason that since the rate of absorption of nicotine from the lozenge is similar to that from other currently available oral NRT formulations, like nicotine chewing gum,6 it is probable that the mouth
spray will also surpass other oral NRT products in terms of craving relief. The nicotine mouth spray provides a potent sensory stimulation, given the instant availability of the dose on the oral mucosa, which may enhance the speed of onset of craving relief.

**STUDIES ON MOUTH SPRAY**

Hansson *et al.* (2012) examined the rate with which nicotine mouth spray relieves urges to smoke, and how it compares with the nicotine lozenges in this respect. A randomized cross-over trial that compared nicotine mouth sprays 2 mg versus nicotine lozenge 2 or 4 mg. Study was done in a clinical pharmacology research unit on 200 volunteer smokers who smoked their first cigarette of the day within 30 min of waking. Subjects abstained from smoking the night before the morning they attended the laboratory. Treatment was administered following 5 h of witnessed abstinence. The primary and secondary outcome measures were, the temptation to smoke was rated before and at 1, 3, 5, 10, 15, 25, 30, 45 min and 1, 1.5, and 2 h after treatment administration. The primary outcome concerned change during the first 1, 3, and 5 min after treatment administration. It was found that nicotine mouth spray achieved greater reductions in craving than either lozenge during the first 1, 3, and 5 min post-administration. On using the mouth spray, half of the users experienced 50% reduction in craving within 3.40 min, while the same effect was achieved within 9.92 and 9.20 min for the 2 and 4 mg lozenge, respectively. Adverse effects with both mouth sprays and lozenges were mostly mild. Hiccups, local irritation, nausea, and dyspepsia were more frequent with spray than lozenge. It was concluded that nicotine mouth spray provides a faster relief of cravings than nicotine lozenge. ²

Tønnesen *et al.* (2012) conducted a study to evaluate self-reported, carbon monoxide-verified continuous abstinence from smoking from week 2 until weeks 6, 24, and 52 in 479 smokers (1 cigarette per day) who were treated with either active (n5318) or placebo (n5161) spray for 12 weeks and low-intensity counseling at three smoking cessation clinics in Denmark and Germany. Active treatment yielded significantly higher continuous abstinence rates than placebo from week 2 until week 6, week 24, and week 52. Most adverse events (AEs) were mild to moderate, and 9.1% of subjects on active spray withdrew due to AEs, compared to 7.5% on placebo. The overall rate of treatment-related AEs was 87.4% with active spray versus 71.4% with placebo spray. Nicotine mouth spray delivered significantly higher 6-, 24-, and 52-week continuous abstinence rates than placebo. ²

**NNS**

The nicotrol inhaler (nicotine inhalation system) consists of a mouthpiece and plastic cartridges, each containing 10 mg of nicotine. One cartridge is inserted into the mouthpiece, and nicotine is released by inhaling. The majority of the nicotine is deposited in the oral mucosa, and maximum blood levels are achieved more slowly when compared to the nasal spray or cigarettes. The nicotine is primarily absorbed through the oral cavity (36%) and the esophagus and stomach (36%), rather than through the lungs (4%). The most common side effects are cough, irritation of the mouth and throat, rhinorrhea, and nausea. The inhaler should be avoided in patients with a history of asthma. Some patients prefer this system because the hand-to-mouth activity mimics cigarette use.

The use of four sprays per hour or a maximum of 80 sprays/day is recommended.

**STUDIES**

Rubenstein (2008): NNS has been one of the most successful forms of nicotine replacement therapy in adult populations. The nasal sprayer has not been studied in adolescent smokers. The objective of this study was to determine the feasibility and utility of using NNS in adolescent smokers who want to quit smoking. 40 adolescent smokers between 15 and 18 years old, who smoked five or more cigarettes daily for at least 6 months, were recruited from several San Francisco Bay area schools from 2005 to 2007. Using a randomized, open-label, 12-week trial, adolescent smokers were assigned to receive either weekly counseling alone (control) for 8 weeks or 8 weeks of counseling along with 6 weeks of NNS. Self-reported smoking abstinence verified by both expired air carbon monoxide and salivary cotinine. There was no difference in cessation rates, the numbers of cigarettes smoked per day or cotinine levels at 12 weeks. 57% of participants stopped using their spray after only 1-week. The most commonly reported side effect was nasal irritation and burning (34.8%) followed by complaints about the taste and smell (13%). It was concluded that the unpleasant side effects, poor adherence, and consequent lack of efficacy observed in our pilot study do not support the use of NNS as an adjunct to counsel for adolescent smokers wishing to quit. ²

Nasal spray can be recommended for 1-2 doses/h for 3-6 months. Its side effects are nasal irritation, irritation of throat, coughing, and watering of eyes. Its contraindications are myocardial infarction or stroke in the past 2 weeks or poorly controlled cardiovascular disease.

**NICOTINE INHALER**

The nicotrol inhaler (now marketed by Pfizer Consumer Healthcare) is a nicotine inhalation system that consists of a plastic cylinder that delivers a nicotine vapor when
warm air is sucked over a porous cartridge in the cylinder.\textsuperscript{9} Absorption occurs buccally and peak plasma concentrations are typically reached within 15 min after inhalation.\textsuperscript{3,10}

Because the inhaler is more similar to a cigarette in appearance and mode of use, abuse/dependence with the inhaler might be greater than that for other oral NRTs such as nicotine gum, lozenge, or micro tab. On the other hand, despite its name, the product provides buccal not lung absorption.\textsuperscript{3,10}

As a result, the nicotine absorption is slow and resultant blood concentrations are low, both of which are associated with smaller behavioral effects and less abuse liability.\textsuperscript{11} Furthermore, the work required to obtain nicotine from the inhaler is much greater than that from smoking. These factors would suggest the inhaler should have little abuse/dependence liability. Currently, many prescribers and smokers believe NRT products are “addicting.”\textsuperscript{12,13}

For example, 55\% of smokers believed it was as easy to become addicted to inhaler as to cigarettes.\textsuperscript{12}

\section*{PRESCRIPTION AND DOSAGE}

The physician prescribing information and patient directions recommend puffing multiple times on a cartridge and using 6-16 cartridges/day for 12 weeks, followed by 12 weeks of tapering (that is, total of up to 6 months). This dosing produces nicotine concentrations similar to that for nicotine gum.\textsuperscript{3,10}

The most common AEs are upset stomach, nausea, diarrhea, and hiccups and these lead to medication discontinuance in 5\% of users.\textsuperscript{14}

Like other NRTs, the inhaler doubles long-term quit rates.\textsuperscript{15}

The incidence of AEs with the inhaler is similar to that for gum, lozenge, and patch.\textsuperscript{16}

In the USA, the inhaler is available only via prescription.

\section*{STUDIES ON NICOTINE INHALERS}

Hughes \textit{et al.} (2005) conducted a study to determine the incidence of off-label use of, abuse of, and dependence on prescription nicotine inhaler. Structured interview about off-label use (that is, use of inhaler for non-cessation reasons or concurrent use of inhaler and cigarettes) and Diagnostic and statistical manual, 4\textsuperscript{th} edition (DSM-IV) and International Classification of Diseases, 10\textsuperscript{th} edition (ICD-10) criteria for abuse and dependence. It was seen that although many used inhaler and cigarettes concurrently at some time (43-55\%), few used inhaler for non-cessation reasons (4-9\%), and few persisted in off-label use (8-16\%). No participant met ICD-10 criteria for harmful use/abuse. Eight subjects (1.4\%) appeared to meet DSM-IV or ICD-10 criteria for dependence on the inhaler, but none were found dependent in a clinical expert interview. It was concluded that although transient concurrent use of inhaler and cigarettes often occurs, use for non-cessation reasons, abuse, and dependence are rare.\textsuperscript{17}

\section*{DISCUSSION}

The dosage and duration of a nicotine inhaler and NNS are four inhalers per day 6-16 cartridges/day for 6 months and 1-2 doses/h for 3-6 months, respectively. For inhaler the initial dose is four inhalers per day, a maintenance dose is four inhalers per day, with gradual tapering of use, and duration of therapy is 8-12 weeks. Whereas, for the nasal spray, the initial dose is four sprays per hour, a maintenance dose is 8-80 sprays/day, with gradual tapering of use, and duration of therapy is 8-12 weeks. The side effects of using nicotine inhaler are local irritation of mouth and throat. Both nicotine inhaler and spray are contraindicated in patients with myocardial infarction or stroke in the past 2 weeks or poorly controlled cardiovascular disease.

\section*{CONCLUSION}

Since the diseases related to tobacco are related to tobacco related toxicants, but not to nicotine \textit{per se}, progress toward this objective will be made most profoundly by reduction in tobacco use, even if nicotine use persists. Hence, tobacco cessation can be carried out effectively with the aid of nicotine replacement therapy. The correct nicotine replacement therapy can be chosen according to the patient’s conditions.

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