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Are smoking cessation methods as successful in reaching long term abstinence rates when used by smokeless tobacco users in the United States

Lorissa Lorenzo-Trujillo
University of the Pacific, lorissa.lorenzo@gmail.com

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By

Lorissa Lorenzo-Trujillo

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BACKGROUND

Rates of Use

Smokeless tobacco is defined as any form of nicotine-containing tobacco that is either chewed or snuffed rather than smoked by the user. In contrast to declining rates of cigarette use in the United States (US), sales and consumption of smokeless tobacco (ST) have continued to increase.[1,2] As of 2016, it was estimated that up to 6.6% of US men, 0.5% of US women and 5.5% of high school students use ST.[3] These rates have increased substantially from the year 2000 when only 4.4% of US men and 0.3% of US women were reported to use ST.[4] Additionally, many cigarette manufacturers have begun producing ST and are marketing it as a less harmful alternative to cigarette use which leads to a concern for dual consumption of both nicotine-containing products.[2] Many studies in the US have reported a moderate to strong degree of association between current smoking and use of ST.[4]

Adverse Effects of Smokeless Tobacco

Although ST is considered less dangerous than cigarettes and other smoked tobacco products, ST use continues to be associated with many poor health outcomes worldwide.[2,5] In the US, its use can lead to nicotine addiction, periodontal disease, cancer and precancerous oral lesions, pancreatic cancer, early parturition, stillbirth, childhood poisoning, hypertension and death from heart disease and stroke.[2,4,6] Twenty-eight carcinogens have been identified in ST; the most abundant group of carcinogens are the non-volatile alkaloid derived tobacco-specific N-nitrosamines and N-nitrosamino acids.[4] Smokeless tobacco acts as an autonomic and hemodynamic stimulus by increasing heart rate, blood pressure and epinephrine levels.[2] Some

studies have even found the effect on heart rate and blood pressure to be more severe in ST use than in cigarette use.[7] Smokeless tobacco products used in the US have a uniquely increased risk of fatal myocardial infarction and fatal stroke when compared to ST from other countries.[8] Overall ST has fewer and less severe adverse health outcomes than cigarette smoking;[2] however, considering the growing rate of ST consumption, health care providers are faced with a difficult task of providing support for their patients who would benefit from ST cessation.

Current Smokeless Tobacco Cessation Recommendations

Despite the increasing rates of ST consumption and the numerous adverse health consequences, medical and oral health professionals in the US have a lack of evidence-based guidelines to assist them in providing effective treatment for ST use.[2] Currently, the U.S. Food and Drug Administration has not approved any cessation products specifically for the treatment of tobacco dependence in ST users. The World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) is a treaty developed by the UN to reduce tobacco use. Unfortunately, this treaty mainly focuses on smoking cessation and does not differentiate between cigarette and ST use.[5] In England, ST cessation guidelines for health professionals were published in 2004. However, ST is used in the UK predominantly by members of the Indian, Pakistani, and Bangladeshi communities. The most commonly used form of ST in this population is called "quid" and has been found to have different physiological and adverse health effects than the ST used in the US.[9]

There are more than 40 different types of ST products consumed around the world.[4] The type of tobacco used is geographically determined. In the US, the principal types of ST are snus

(moist ground tobacco) and chewing tobacco (cut tobacco leaves).[2,10] The type of tobacco used in a particular product has an influence on its pharmacodynamics, pharmacokinetics, sensory and behavioral involvements, adverse health outcomes, dependence patterns, and potential responses to cessation methods.[2,4,8,10]

The three main cigarette cessation methods used in the US include nicotine replacement therapy (NRT), non-nicotine pharmacotherapies (varenicline and bupropion) and behavioral therapies. Smokeless tobacco specific recommendations are not currently available for health care providers in the US. This article examines whether the listed cigarette cessation methods are equally effective in reaching long-term abstinence rates when used by ST users, for which long-term abstinence is defined as zero ST consumption for 6 months or more.

COMPARING SMOKLESS TOBACCO AND CIGARETTES

Absorption and Distribution

There are many factors that determine the pharmacokinetics and pharmacodynamics of nicotine-containing products. The route of administration is one of the most important factors when evaluating a tobacco product's effects, especially when considering absorption.[4,10] Significant differences between nicotine absorption rates from smoked tobacco versus ST products have been well-documented.[4] It has been postulated that these differences among nicotine products may determine the dependence patterns and response to cessation methods.[10]

Multiple studies have shown that nicotine absorption and therefore nicotine-dosing capability varies between products.[4,7] The difference in nicotine absorption from ST use versus

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cigarette use is determined primarily by nicotine content and amount and frequency of use.[4] One

study analyzed 17 brands of ST in the US and found that the nicotine content ranged anywhere

from 0.47% dry weight to 3.34% dry weight.[4] Comparatively, the average Marlboro Light's®

nicotine content is approximately 2.09% of dry weight.[11] Although the nicotine content is quite

similar between ST and cigarette products, the amount and frequency of use differ greatly.

Duration of use of ST is approximately 20-40 minutes whereas the duration of cigarette use is

approximately 5-7 minutes.[10] For this reason, those who use ST are exposed to nicotine for longer

periods of time and are therefore absorbing a higher level of nicotine content overall.

Additionally, absorption kinetics of ST differ greatly from cigarettes.[10] Absorption of

nicotine from smoking occurs rapidly through the pulmonary circulation; peak blood levels are

achieved quickly.[10,12] Nicotine levels then decline rapidly once the cigarette is finished.[12]

Comparatively, absorption of nicotine from ST occurs through mucous membranes and thus

declines at a much slower rate. [10,12] One study proposes that nicotine from ST continues to

absorb into systemic circulation even after the product is removed from the mouth. It is

suggested that the continued absorption is due to a slow release of nicotine from mucous

membranes as well as from nicotine that has been swallowed. For these reasons, overall

absorption of nicotine is twice as great from ST when compared to cigarettes.[12]

These differences in absorption lead to distinctive cardiovascular effects and dependence

patterns.[12] Absorption of nicotine from cigarette use occurs as arterial boluses resulting in

significant peaks and valleys in the nicotine concentration with each puff from a cigarette. These

peaks and valleys in nicotine concentration are not observed in those who use ST.[10] The slower

absorption of nicotine from ST use, consequently allows the central nervous system to be

presented with a steadier rate of nicotine distribution as opposed to the pulsed increases seen with cigarette use. The magnitude of cardiovascular response is correlated directly with the rate of decline in nicotine blood levels. Heart rate and blood pressure remain elevated for longer periods of time in ST users than in cigarette users resulting in a greater overall cardiovascular effect from ST use. [7,12] Additionally, the propensity towards tobacco addiction is associated with the rate at which nicotine is distributed to the CNS along with the behavioral and sensory stimuli that accompany tobacco use.[10,12]

Sensory and Behavioral Involvement

Repeated use of tobacco products is related to nicotine as well as non-nicotine factors. Sensory stimulation and behaviors that accompany ST use differ from those associated with cigarette smoking. Sensory stimulation from cigarette use is considered very rich, involving factors such as visual smoke, taste, smell, and impact on throat and airways. It is often used as a social element as a form of bonding. On the other hand, sensory stimuli from ST is associated more with taste, smell, sucking, chewing, as well as pressure and a burning sensation on the mucosa where the product is placed.[10] These sensory and behavioral differences among nicotine-containing products may reflect the differences in response to cessation methods.

EFFICACY OF CESSATION METHODS

Nicotine Replacement Therapy

Nicotine replacement therapy (NRT) consists of products designed to deliver nicotine to the body in a form that does not involve smoking or the ingestion of any tobacco-containing

products. It comes in 16-hour and 24-hour transdermal patches, 2 or 4 mg chewing gum, and 1, 1.5, 2, and 4 mg nicotine lozenges, among other formulations. The goals of NRT are to reduce withdrawal symptoms and to provide a coping mechanism, making tobacco products less rewarding.[13]

Many studies support the use of NRT for cigarette cessation; it is considered a first-line treatment modality for anyone who wants to quit smoking.[5,14,15,16] Conversely similar evidence supporting the use of NRT in ST cessation is lacking. In cigarette users, NRT is found to reduce withdrawal symptoms and therefore increase abstinence rates.[14] When used by those who consume ST, a reduction in withdrawal symptoms is also observed. However, despite the reduction in withdrawal symptoms, abstinence rates do not improve when compared to placebo.[14] This failure contradicts the premise that nicotine replacement is the primary mechanism of action for achieving abstinence from tobacco. In most studies, NRT has not been found to increase abstinence rates for ST users regardless of formulation or dose.[2,5,14] Nicotine gum may, in fact, facilitate lapse or relapse in ST use.[14] One study that examined the use of NRT in ST cessation did find a potential benefit for use of lozenges when combined with coach calls.[1] The evidence from this study suggests that the lozenges initially helped participants with withdrawal symptoms and the coach calls provided social support for continued abstinence which allowed the combination to be more successful than either coach calls or lozenges alone. Unfortunately, this study is flawed in that it did not use biochemical validation of abstinence, hence possibly overestimating true cessation rates.

NRT may not be as successful in ST cessation when compared with cigarette cessation for several reasons. Smokeless tobacco delivers a higher overall nicotine concentration than

cigarettes. The dosage of nicotine provided in NRT may be too low for ST users. Additionally, there are similarities in the behavior (sucking and chewing), the rate of absorption and the distribution patterns of oral NRT and ST. Due to the behavioral similarities of using ST and oral NRT in addition to the initial alleviation of withdrawal symptoms, it's possible that oral NRT products produce a priming effect that facilitates relapse and that ST users do not effectively learn new behavioral or coping skills that would substitute for ST use.

Bupropion

Bupropion is an atypical antidepressant that has multiple actions in the brain involving dopamine and noradrenaline pathways and is a non-competitive nicotine receptor antagonist. It is also believed to inhibit the firing of adrenergic neurons in the locus coeruleus which is the region of the brain responsible for the stress and panic associated with withdrawal from nicotine. A typical course for cigarette cessation is 300 mg per day for 7-8 weeks, beginning a week prior to the designated quit date.[17]

In cigarette users, bupropion is generally considered as effective as NRT in achieving long term abstinence rates.[5,16] One study showed bupropion increases abstinence rates in cigarette users by 7% when compared to placebo.[5] Although other studies have mixed results, it is still considered a first-line pharmacotherapy for smoking cessation. In ST users, however, bupropion has not been shown to be effective in reaching long term abstinence rates.[2,5] It is important to note that bupropion has not been studied without the use of behavioral support.[5]

It is possible that bupropion is less effective in ST users than in cigarette users due to the differences in the absorption and distribution characteristics of these products. Smokeless

tobacco users are exposed to nicotine for longer periods of time leading to a more constant plasma level than those who smoke cigarettes. With a more constant and extended nicotine plasma level, compared to cigarette users, ST users may have a lower adrenergic reserve available for the bupropion's action. It is this adrenergic response in the locus coeruleus that is believed to be responsible for withdrawal symptoms. With cigarette use, there is sufficient time between nicotine dosing periods to rebuild the adrenergic reserve. Therefore, in cigarette users, the bupropion has the opportunity to attenuate the effects of the adrenergic response and reduce the withdrawal symptoms. It's also possible that the constant nicotine levels in ST may desensitize nicotine receptors making them unavailable to bupropion. In cigarette users, however, the lack of constant stimulus by nicotine may actually prevent desensitization of the nicotine receptors allowing the bupropion to be more effective.

Varenicline

Varenicline is a partial agonist designed to bind with high affinity to the alpha-4 beta-2 subunits of nicotine receptors where its binding produces agonist activity while simultaneously preventing nicotine from binding to these receptors. Through these actions, varenicline is believed to reduce symptoms of nicotine withdrawal and reduce the rewarding aspects of tobacco use.[18] A standard course of treatment for cigarette cessation is 1 mg per day beginning 1 week before the designated quit date then 11 weeks at 2 mg per day.

Varenicline is generally considered one of the most effective tobacco cessation products.[16] In cigarette smokers, varenicline has been found to increase abstinence rates by 131% when compared to placebo. In ST users, however, it does not appear to be as effective. The

evidence from the same study showed that varenicline only increased long term abstinence rates by 34% when compared to placebo.[2] Although it may not be as effective in reaching long term abstinence in ST users, it does increase the likelihood of recovery after a lapse.[19] As with bupropion, all varenicline studies involved some form of behavioral support.[5]

The peaks and valleys in nicotine concentration observed in cigarette users are not observed in ST users. This difference may explain why varenicline is less effective in ST cessation than in cigarette cessation. Varenicline is a partial agonist which binds to the same receptors as nicotine consequently preventing the nicotine molecule from binding. In ST, the higher nicotine concentration may lead to greater occupancy or desensitization of the nicotine receptors and therefore may not allow the varenicline molecule the opportunity to bind. On the other hand, the valleys in nicotine concentration observed in cigarette use may allow opportunity for the drugs to occupy the receptor and therefore more effectively block the action of the nicotine molecule.

Behavioral Interventions

A wide variety of behavioral interventions for the treatment of tobacco cessation is available. Some more widely accepted options include brief advice and face-to-face behavioral support. Brief advice involves a health-care worker raising the topic of smoking or ST use with a patient, advising the patient to stop and/or offering support and follow up. Face-to-face behavioral support, on the other hand, is a bit more intensive. It may include advice, discussions, encouragement or activities designed to assist in the cessation of tobacco and may be delivered

individually or in groups. Other behavioral interventions may include printed self-help materials, automated text messages, telephone counseling, oral examination and interactive websites.

It is difficult to directly compare behavioral interventions because the components of interventions that contribute to their impact are not clear.[2] In general, behavioral interventions vary with efficacy in abstinence rates.[2] Evidence mainly supports using some form of behavioral intervention regardless of the use of pharmacotherapy.[16] Even brief advice from a health-care worker, compared to doing nothing, has been found to promote smoking cessation and increase abstinence rates of cigarette users by 2%.[5] However, insufficient evidence prevents conclusions about brief advice to promote ST cessation.[5] Face-to-face behavioral support has been found to be effective in both cigarette and ST users.[5] Behavioral interventions incorporating telephone support and oral examination also appear to be effective in reaching long term abstinence in ST users.[2]

It is unclear whether behavioral interventions alone are more successful when used in cigarette smokers compared to ST users. Regardless of the tobacco product being used, behavioral intervention appears to play an important role in reaching long term abstinence rates. Nicotine itself is a weak reinforcer but becomes stronger when the drug is paired with environmental cues. These reasons likely explain why behavioral intervention plays such an important role in the cessation of all nicotine-containing products. While pharmacotherapy may assist with the physiological symptoms of withdrawal, behavioral interventions provide the social support for patients to help them identify and challenge the environmental cues that trigger cravings.

CONCLUSION

If the cessation methods are ranked from the most to the least successful, the list would be in the same order for both ST and cigarette use. However, the likelihood of each of these cessation methods achieving long term abstinence rates appears to be higher in cigarette users than in ST users overall. Furthermore, it is unclear if NRT and bupropion are effective at all in ST cessation. In fact, it's possible that NRT may actually promote relapse in ST users. In cases where NRT was found to be effective, it was combined with behavioral interventions. Varenicline appears to be the most effective pharmacotherapy for the treatment of ST dependence; however, it too must be combined with behavioral interventions to achieve the best results. Regardless of the cessation method used, it is important to consider using some form of behavioral intervention as it appears to increase abstinence rates in both ST and cigarette users.

Currently, healthcare providers in the US make the same recommendations for cessation of both ST and cigarette use. The conclusions derived from the evidence in these studies do not necessarily change the recommendations that providers will give to their patients. The findings should, however, make clinician expectations of patients' success more realistic when using cigarette cessation methods in ST users.

IMPLICATIONS FOR FURTHER RESEARCH

More research is necessary to determine the most effective way for ST users to achieve long term abstinence rates. Since, compared to cigarette use, ST use leads to more sustained and higher nicotine levels through its continuous absorption, determining the most effective NRT dose, formulation, and duration of therapy is necessary. Additionally, many studies support the

use of NRT combined with non-NRT pharmacotherapies for cigarette cessation, whereas research on this combination therapy in ST cessation is lacking, but would be beneficial.

Due to the differences in nicotine plasma concentrations between ST and cigarette users, the possibility that non-NRT pharmacotherapies would be more effective if initiated after the patient has discontinued ST for a short period should be explored. In these proposed studies, the patient may achieve an initial discontinuation phase by using NRT, which may lower the plasma concentration of nicotine, allowing for the non-NRT pharmacotherapies to be more effective. Starting varenicline after an initial discontinuation phase may allow better binding between varenicline and the nicotine receptors. Analogously, starting bupropion after an initial discontinuation phase may allow either the adrenergic reserve to restore or permit receptor sensitization to return, giving bupropion the opportunity to have a more robust effect on the withdrawal symptoms.

Lastly, behavioral intervention methods and efficacies vary widely. Future research should aim at identifying the most effective core components of behavioral interventions for the treatment of ST dependence.

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