

## **7.5.2-1: INITIAL – USERS’ BEHAVIOR – LITERATURE SUMMARY**

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## List of Abbreviations

AOR	adjusted odds ratio
AUC	area under the concentration-time curve
AUTOS	Autonomy Over Smoking Scale
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C <sub>max</sub>	maximum measured concentration
CO	carbon monoxide
DIS-IV-ND	Nicotine Dependence module of the Diagnostic Interview Schedule, 4 <sup>th</sup> Edition
FTND	Fargeström Test of Nicotine Dependence
(m)FTND	(modified) Fargeström Test of Nicotine Dependence
FTND-ST	Fargeström Test of Nicotine Dependence for smokeless tobacco users
FTQ	Fargeström Tolerance Questionnaire
FTQ-ST	Fargeström Tolerance Questionnaire for smokeless tobacco users
(m)FTQ-ST	(modified) Fargeström Tolerance Questionnaire for smokeless tobacco users
HONC	Hooked on Nicotine Checklist
ICSS	intracranial self-stimulation
LC	locus coeruleus
MAO	monoamine oxidase
MRTPA	modified risk tobacco product application
MST	moist snuff tobacco
MTF	Monitoring the Future Survey
N/A	not applicable
NHANES	National Health and Nutrition Examination Survey
NRT	nicotine replacement therapy
NS	not statistically significant
NSDUH	National Survey on Drug Use and Health
NYTS	National Youth Tobacco Survey
OCT	other combustible tobacco products
OR	odds ratio
OSSTD	Oklahoma Scale for Smokeless Tobacco Dependence
PD	pharmacodynamic
PK	pharmacokinetics
POMS	Profile of Mood States
QSU	Tiffany-Drobes Questionnaire of Smoking
RR	risk ratio
ST	smokeless tobacco
TH	tyrosine hydroxylase
T <sub>max</sub>	time of the maximum measured concentration
TOTLTOB	total tobacco intake in terms of cigarettes per day
TTFU	time to first use
TUS-CPS	Tobacco Use Supplement- Current Population Survey
U.S.	United States
VAS	visual analog scale

### **7.5.2-1. LITERATURE SUMMARIZING THE EFFECT OF SMOKELESS TOBACCO ON SMOKELESS TOBACCO USE BEHAVIOR AMONG CURRENT TOBACCO USERS**

The Family Smoking Prevention and Tobacco Control Act and the Food and Drug Administration’s Modified Risk Tobacco Product Applications (MRTPA) 2012 Draft Guidance, Section VI(A)(2), require assessment of the following tobacco use behaviors in current users:

- the likelihood that current tobacco product users will start using the product;
- the likelihood that tobacco users who adopt the product will switch to or switch back to other tobacco products that present higher levels of individual health risk;
- the likelihood that consumers will use the product in conjunction with other tobacco products;
- the likelihood that consumers who may have otherwise quit using tobacco products will instead use the product; and
- the likelihood that consumers will use the product as intended or designed.

The guidance also requires assessment of the following:

“...the abuse potential and the potential for misuse of the product as compared to other tobacco products on the market...and actual use of the product.”

The abuse potential of a tobacco product is defined as “the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product. Physical dependence is characterized by the development of tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping use of the tobacco product. Psychological dependence is characterized by persistent tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and inability to abstain consistently.”

To assess how the candidate modified risk tobacco products may affect user behavior as outlined in Section VI(A)(2) of the MRTPA 2012 Draft Guidance, this section summarizes the published scientific literature on smokeless tobacco (ST) use behaviors and abuse potential of ST products typically marketed in the (U.S.).

Altria Client Services LLC conducted a comprehensive literature search to identify published information relevant to tobacco use behaviors of tobacco product users with regard to the effects of ST products (i.e., initiation, actual use, dual use, switching, cessation) and with regard to abuse potential of ST products, which includes misuse/abuse, subjective effects, and pharmacokinetics (PK) of ST products, withdrawal and dependence, and nonclinical studies of ST and its extracts. A description of our literature search and review process is presented in [Section 7.5.1](#) of this MRTPA. This review is limited to studies of ST products used in the U.S. that were published between through December 2014. From this search, a total of 6,742 publications were identified, and, after a comprehensive and in depth critical review, 537 were determined to be in scope. These publications were further reviewed to

assess which specific category(ies) in the MRTPA Draft Guidance each article addressed. Reports published shortly after the date of our last search were included in this review when deemed to be significant contributions to this body of research. An updated literature review was conducted to bridge the original review to February 2017, and updated findings informing ST user behavior are presented in Section 7.5.2-2.

The initial literature search on use behaviors and abuse potential was performed and any additional publications were identified through review of the reference lists within the identified publications. As applicable, more specific searches were conducted to identify publications and national survey data on cigarettes in order to make relative comparisons with cigarette smoking. The studies reported in the literature present a diverse set of methodologies including surveys, interviews, questionnaires, clinical trials, cross-sectional studies, longitudinal studies, field studies, and secondary analyses of data from nationally representative surveys. The number of subjects evaluated in these studies ranged from as few as eight (Benowitz, Jacob III, & Yu, 1989) to nationally representative weighted samples (e.g., (Fix et al., 2014; Saunders & Geletko, 2012)). Participants in these studies included school-age adolescents, college students, college athletes, Native Americans, military personnel, professional athletes, and adult males and females of the general public. The ST products evaluated are most commonly described as ST (nonspecific), snuff, or chewing tobacco. Since moist snuff tobacco (MST) products comprise a significant proportion of the ST products available in the U.S. market and have done so for many years, the scientific observations based on the general category of ST products are considered generalizable to MST (Section 7.5.6-1 and Section 7.5.6-2).

While there is a large body of literature evaluating ST use behaviors in the U.S., these investigations were generally not prospectively designed to assess the tobacco use behaviors identified in the MRTPA 2012 Draft Guidance. For example, to the best of our knowledge, there are no studies directly evaluating the likelihood that users who may have otherwise quit using tobacco products will instead use ST (Section 7.5.2-1.4). Although this is a limitation of the current literature review, the large volume and quality of publications conducted with ST products manufacture

d in the U.S. indicate that the data sets within the current literature characterizing ST use behaviors are sufficiently robust to inform the issues raised by the Food and Drug Administration in the MRTPA 2012 Draft Guidance. Within each tobacco use behavior section, the strengths and limitations of the available literature are presented.

On the basis of the current published literature with U.S. ST products, the following observations can be made about tobacco use behaviors in current users and the abuse potential of ST:

- The likelihood that current tobacco product users will start using the product
  - Initiation of regular ST use in current tobacco users (i.e., cigarette smokers) is far less common, in terms of switching to ST only or dual use (i.e., cigarette smoking and ST use), than the initiation of regular cigarette use in ST users. Although there are some reports of current tobacco users initiating ST use, this often appears to be an approach to smoking cessation. In these cases, ST may provide a

supplementation or substitution of nicotine intake for cigarette smokers (Section 7.5.2-1.1).

- The likelihood that tobacco users who adopt the product will switch to or switch back to other tobacco products that present higher levels of individual health risk
  - The available evidence on switching behaviors is mixed. Tobacco switching behaviors appear to be rather infrequent (< 4 percent), but when switching does occur, it is more likely to be from ST or dual use to cigarettes only. While there is evidence that a proportion of ST users may switch to cigarettes when they cannot or do not want to use ST, ST may also serve as a quitting method in some cigarette smokers. Therefore, there is little overall evidence to support switching to cigarettes as being the predominant outcome of ST use (Section 7.5.2-1.2).
- The likelihood that consumers will use the product in conjunction with other tobacco products
  - The prevalence of dual use of ST and cigarettes is lower than that of exclusive cigarette smoking; however, the prevalence of concurrent cigarette smoking in ST users is higher than the prevalence of concurrent ST use in cigarette smokers. Consistent with the demographic characteristics observed in exclusive ST users, dual users are more likely to be younger, unmarried, white males with lower educational background and socioeconomic status. Dual users may exhibit more signs of nicotine dependence than single tobacco (cigarette or ST) product users. Dual users generally smoke fewer cigarettes than exclusive smokers, supporting the notion that in some dual users one tobacco product serves as a substitute for another product. While dual users are less likely to stop all tobacco use over time, they appear more likely to reduce smoking intensity (Section 7.5.2-1.3).
- The likelihood that consumers who may have otherwise quit using tobacco products will instead use the product
  - There is no single study that prospectively and specifically examines the likelihood that consumers who may have otherwise quit using tobacco products (in this case “imminent quitters” of cigarettes) will instead use ST; however, the literature supports that some cigarette smokers use ST to cut down on smoking, as an alternative to quitting tobacco altogether, or to help quit smoking. Although use of ST appears to be a prevalent self-reported approach to altering smoking behaviors, there is no overall conclusive evidence to determine if ST use promotes or hinders cessation of smoking in the U.S. (Section 7.5.2-1.4).
- The likelihood that consumers will use the product as intended or designed
  - ST is a consumer product without specific directions for use or application; therefore, the likelihood that consumers will or will not use the product as intended or designed cannot be effectively assessed (Section 7.5.2-1.5).
  -

- The abuse potential and the potential for misuse of the product as compared to other tobacco products on the market

Based on clinical and nonclinical studies, nicotine is considered the primary pharmacological determinant of the abuse potential of ST products, similar to other tobacco products. The available evidence suggests that the abuse potential of ST is higher or similar to that of nicotine replacement therapy (NRT), but consistently lower than that of cigarettes. The limited number of reports suggests misuse and abuse of tobacco products, including ST, is very rare. Although several nonpharmacological factors contribute to tobacco use initiation (e.g., availability, peer influences), initiation of ST use is consistently and significantly lower than that of cigarettes, suggesting the intrinsic reinforcing efficacy is lower for ST. Clinical trials show notable differences in subjective effects (e.g., satisfaction, liking, craving, withdrawal suppression) between ST and cigarettes, supporting that ST has significantly lower abuse potential than cigarettes, although greater than NRT; such differences in pharmacodynamic (PD) effects are congruent with the lower rate of nicotine exposure with ST compared with that for cigarettes. Finally, ST is observed to have a lower dependence potential, as seen by milder withdrawal signs and symptoms in abstinent ST users, than that for smokers and higher overall cessation rates in ST users than that for cigarette smokers (Section 7.5.2-1.6).

Sections 7.5.2-1.1 through 7.5.2-1.6 address the topics identified in Section VI(A)(2) of the MRTPA 2012 Draft Guidance using a variety of scientific studies conducted with ST in order to substantiate these conclusions. An updated literature review of these topics is provided in Section 7.5.2-2.

### **7.5.2-1.1. The Likelihood that Current Tobacco Users Will Start Using the Product**

#### **7.5.2-1.1.1. Overview**

Section 7.5.2-1.1 focuses on the likelihood that current tobacco users will initiate the use of ST. For the purposes of this review, “current tobacco users” were limited to current cigarette smokers (i.e., pipes, cigars, hookah and other tobacco products were not included) because cigarette smoking represents the predominant form of tobacco use in the U.S. (Center for Behavioral Health Statistics and Quality, 2015). While it was initially expected that a larger body of literature would be available on the likelihood of ST use initiation in current smokers, upon review of the literature, it was determined that, regardless of comparison group, relatively little information is available on the rates of initiation of ST use in current tobacco users as compared with initiation patterns in nonusers (Section 7.5.3-1 and Section 7.5.3-2). This is likely because initiation of regular ST use in current smokers was found to be far less common both for those switching to using ST only and for those switching to dual use, particularly when compared with the initiation of regular cigarette use in former ST users (Tomar, 2003; S.-H. Zhu et al., 2009).



#### 7.5.2-1.1.2. Literature Review Results

The literature search, as described in [Section 7.5.1](#), did not yield any publications that reported specifically on the initiation of ST use in current smokers. However, 11 articles were identified within other categories of behavior (e.g., switching behaviors, intercepting and quitting effects) that included relevant information facilitating our discussion. Participants in these 11 studies included adolescents, young adults, as well as former and current adult smokers. The number of participants evaluated in these studies ranged from 20 ([R. G. Boyle, Gerend, Peterson, & Hatsukami, 1998](#)) to 116,395 ([Henley et al., 2007](#)).

#### 7.5.2-1.1.3. Summary of Literature

Two longitudinal studies collected information on the patterns of tobacco use behavior, including the initiation of ST use in current smokers at follow-up. In the first study, a 4-year longitudinal study of 3,996 adolescent males, most exclusive smokers (78.7%) were still only smoking at follow-up; whereas, only 0.8% and 3.6%, respectively, had switched to ST exclusively or became dual users (i.e., user of both cigarettes and ST; ([Tomar, 2003](#))). Similarly, a longitudinal, nation-wide survey study (1-year follow-up) reported that for adult males (n = 1,387), quitting one form of tobacco and initiating another were infrequent, with only 0.3% of 1,105 subjects reporting initiating regular ST use after smoking. In the same study, male dual users (48 subjects) switched to cigarettes alone more often than to ST alone (37.0% vs. 4.9%), but continued to use both products most often (45.0%) ([S.-H. Zhu et al., 2009](#)). Although female ST use was reported far less often (24 subjects), most female tobacco users followed the same pattern, with 3.2% initiating cigarette use after using ST and 0% and 0.1% of smoking females becoming ST users or dual users, respectively. Based on these two longitudinal studies, the initiation of smoking or dual use in ST users may be higher than that of smokers initiating ST use, a finding consistent with reports of higher prevalence of smoking in ST users (as compared with ST use in smokers).

In contrast to the studies described above, a smaller number of studies report a relationship between current smoking and initiation of regular ST use. In a study of 1,084 high school athletes, [Walsh et al. \(2003\)](#) reported that the strongest predictor of ST initiation was being a current smoker, with current smokers approximately seven times more likely to initiate ST use than nonsmokers (odds ratio [OR] = 7.25, 95% confidence interval [CI]: 3.07-17.1). A study in 614 Native American women reported a similar proportion of current ST users who were former smokers (27%) as current smokers who were former ST users (33%; ([Spangler, Dignan, & Michielutte, 1997](#))). This relationship has also been reported in a study of 2,714 adolescents, where the probability of onset of ST use was higher in regular smokers (0.27%) than nonusers (0.04%; ([Dent, Sussman, Johnson, Hansen, & Flay, 1987](#))).

[Riley et al. \(1989\)](#) also found a strong relationship between smoking and initiation of regular ST use in a sample of 3,725 high school students ( $\chi^2 = 136.32$ ,  $p < 0.0001$ ); however, in some cases (6%), initiation was related to using ST to quit smoking. Furthermore, those individuals reporting ST use three or more times per day were more likely to report their ST use was influenced by trying to quit cigarettes compared to less frequent ST users (< 3 times per day;  $\chi^2 = 30.66$ ,  $p < 0.005$ ). Consistent with this finding, there is a body of evidence suggesting that initiating ST use in current smokers is a method to aid in smoking cessation (see [Section](#)

7.5.2-1.4). In addition, [Popova et al. \(2013\)](#) reported that in a sample of 1,836 current or recently former (< 2 years) adult smokers, 7.4% had begun use of ST to quit smoking. One study analyzed the demographic characteristics of 12, 400 current tobacco users who are likely to initiate ST use as a method of quitting cigarettes and reported that younger (18-24 years), male, white, current someday smokers who are less nicotine dependent (as assessed by time to first use [TTFU] > 30 min) are more likely to initiate ST use to aid in quitting cigarettes than to use other methods ([Schauer, Malarcher, & Babb, 2014](#)).

#### **7.5.2-1.1.4. Summary**

Overall, initiation of regular ST use in current tobacco users (i.e., cigarette smokers) is far less common, both in terms of switching to ST only or dual use, than the initiation of regular cigarette use in ST users. Although there are some reports of current tobacco users initiating ST use, this appears to be primarily as an approach to smoking cessation ([Kasza et al., 2014](#); [Riley et al., 1989](#)). In these cases, ST may provide a supplementation or substitution of nicotine intake for cigarette smokers. Additional information on the prevalence of ST initiation in current tobacco users is included in Sections 7.5.2-1.2 through 7.5.2-1.4.

### **7.5.2-1.2. The Likelihood that Tobacco Users Who Adopt the Product Will Switch to or Switch Back to Other Tobacco Products that Represent Higher Risk**

#### **7.5.2-1.2.1. Overview**

Section 7.5.2-1.2 focuses on the risk that cigarette smokers who switch to ST might be more likely to switch back (relapse) to higher risk tobacco products such as cigarettes. Within the literature, the behavior in which individuals switch from using a lower risk tobacco product to a higher risk tobacco product is commonly referred to as gateway. Therefore, for ease of review, the switching behavior described in the title has been abbreviated as gateway.

To our knowledge, there is no single study directly and prospectively evaluating the likelihood that ST serves as a gateway to higher risk tobacco product use in current tobacco users. While there are a few longitudinal studies reporting on switching behaviors, the majority of available studies do not address this question specifically and are cross-sectional in nature, thereby limiting tobacco use trajectory assessment. Other issues include potential recall bias and incorrect self-reported tobacco user classification. In addition, the populations studied differ in their motivations to use or quit tobacco, making it difficult to compare data across studies. However, several of the studies used large sample sizes, including nationally representative samples, and reported data on switching and relapse to cigarette use.

Overall, the available evidence is mixed. Tobacco switching behaviors in exclusive users appear to be rather infrequent ([Henley et al., 2007](#); [Wetter et al., 2002](#); [S.-H. Zhu et al., 2009](#)), but when switching does occur, it is more likely to be from ST or dual use to cigarettes ([S.-H. Zhu et al., 2009](#)), and a proportion of ST users may switch to cigarettes when they cannot or do not want to use ST ([R. G. Boyle et al., 1998](#); [Chakravorty & Chakravorty, 1997](#)). However, smokers who use ST as a quit method may have a lower rate of relapse to smoking than those who use other quit methods (e.g., ([Brad Rodu & Phillips,](#)

2008); see also Section 7.5.2-1.4). Therefore, the evidence from current literature is inadequate to infer the presence or absence of a causal relationship between ST use and subsequent cigarette use in current tobacco users.

#### **7.5.2-1.2.2. Literature Review Results**

The literature search yielded 12 publications reporting on tobacco switching behaviors of smokers or dual users. Participants in these studies included primarily male college students and adults. The number of participants evaluated in these studies ranged from as few as 20 (R. G. Boyle et al., 1998) to as many as 116,395 (Henley et al., 2007).

#### **7.5.2-1.2.3. Longitudinal Studies**

Three longitudinal studies evaluated smokers’ or dual users’ behaviors related to switching between tobacco products.

Zhu et al. (2009) analyzed population data based on a U.S. national survey (N = 15,056 adults) over a 1-year period, and reported that quitting one form of tobacco and switching to another was infrequent among adult males; if there was a switch, it was more likely to be from ST to cigarettes than from cigarettes to ST (3.9% vs. 0.3%). Male dual users switched to cigarettes alone more often than to ST alone (37.0% vs. 4.9%), but continued to use both products most often (45.0%). Female ST users were much lower in number than males, but switching behaviors followed the same pattern (3.2% of ST-only female users became cigarette smokers and none became dual users; whereas, no female cigarette smokers switched to ST only and 0.1% became dual users).

Henley et al. (2007) also found low rates of switching to other tobacco products. After an analysis of Cancer Prevention Study II data, restricted to 116,395 men aged  $\geq 30$  years who were former smokers, the authors found that 3 percent of those who had switched to ST relapsed to cigarettes after a 10-year period and 1.4 percent of all tobacco quitters relapsed to cigarettes. Because the assessment of switching behavior was not an objective of the study, the difference in relapse rate between switchers and all tobacco quitters was not evaluated statistically.

O’Hegarty et al. (2012) analyzed switching behaviors in 3,284 adolescents. In comparing exclusive cigarette smokers with dual users over a 1-year period, the data showed that 37% of baseline dual users continued smoking cigarettes and using ST, 36.6% switched to cigarettes alone, and 17.9% had quit both products. In contrast, 73.4% of baseline exclusive smokers continued to smoke only, 5% switched to dual use, 1.6% switched to ST only, and 20.0% had quit all tobacco. The unadjusted analysis showed a similar proportion of continued smoking for both groups (73.6% for dual users and 78.4% for cigarette smokers); however, when factors not statistically significant for continued smoking (e.g., depression, delinquency) were removed from the model, dual users were less likely to continue smoking than exclusive smokers at the 1-year follow-up (OR = 0.71, 95% CI: 0.52–0.98).

#### **7.5.2-1.2.4. Cross-Sectional Studies**

Six cross-sectional studies evaluated smokers’ or dual users’ behaviors related to switching between tobacco products.

After analysis of 1998 National Health Interview Survey tobacco use history data for 13,865 males aged 18 years or older, [Tomar \(2002\)](#) found a higher cigarette smoking prevalence among former (39.4%) and some-day (38.9%) ST users than that among daily ST users (19.2%) or never users (25.4%). In addition, 2.5% of men were former ST users who currently smoked cigarettes, whereas 0.9% were former cigarette smokers who currently used ST (1.1% were current dual users). These results suggest that ST users are more likely to switch to smoking; however, this cross-sectional survey did not ask age about first use of ST products, which is critical to understanding gateway behaviors ([Kozlowski, O'Connor, Edwards, & Flaherty, 2003](#)).

[Chakravorty and Chakravorty \(1997\)](#) surveyed 950 male undergraduate tobacco users and former tobacco users and determined that 24% of former ST users reported smoking cigarettes as an aid to quitting ST, while 6% of ex-smokers said they used ST to help them quit ( $p < 0.01$ ). In this survey, former ST users were significantly more likely to report current cigarette smoking than former smokers were to report current ST use (12% vs. 0.01%, respectively;  $\chi^2 [1, N = 877] = 46.3, p < 0.01$ ).

Although most research related to ST use focuses on male populations due to low proportion of females who use ST, two studies explored ST use in females. [Cohen-Smith and Severson \(1999\)](#) (59 male and 51 female adult ST users) found that only 1 of the 51 women interviewed had never tried cigarettes and 89.8% of men were also current or former smokers; however, the study did not determine whether ST was a gateway to cigarette smoking or the reverse (or co-occurred), and used a small sample size. [Boyle et al. \(1998\)](#) studied an even smaller sample of ST-using young women ( $n = 20$ ), the majority of whom had started tobacco use by experimenting with cigarettes (60%). Of those who had experience with cigarettes, 10% were regular smokers, 35% occasional smokers, 30% had tried smoking, and 25% were ex-smokers. A total of 65% of the sample had reported using cigarettes as an alternative when unable or unwilling to use ST, while 25% reported switching to ST from cigarettes to help quit smoking.

[Rodu and Phillips \(2008\)](#) found that, of the 43 men (equivalent to a U.S. population estimate of 358,668) who had switched to ST to quit cigarettes, 73% became former smokers, which was higher than the proportion of those quitting successfully with the nicotine patch (35%), gum (34%), inhaler (28%), or nasal spray (0%). About 42% of men who switched from cigarette smoking to ST use also stopped smoking all at once, which was higher than those who used bupropion (8%), the nicotine patch (18%), or nicotine gum (19%). Of those who decreased cigarette smoking more gradually, the proportion using ST (15%) was also higher than that for other methods (3% with bupropion and 4% with the nicotine patch). In addition, these researchers found that 54% of those who had switched from cigarette smoking to ST use were not using any tobacco when surveyed. The proportion of those who had abstained from tobacco for 10 years or more was substantially higher for those who switched to ST (48%) than for those who used other methods (13% with nicotine patch, 39% with gum, and 5% with bupropion). It should be noted that subjects could select more than one quit method on the survey; therefore, the results are not mutually exclusive.

[Hatsukami et al. \(1999\)](#) reported that in a subset of 402 treatment-seeking ST users (subset sample size unverifiable), 14.0% who had ever smoked cigarettes used cigarettes as an aid to

quitting ST (24.4% among ever regular smokers); however, 25.9% of ever smokers had used ST to quit cigarettes (55.3% among ever regular smokers). This sample was considered biased as regular dual users were excluded from the analysis.

#### **7.5.2-1.2.5. Clinical Studies**

Two clinical studies reported on smokers’ or dual users’ behaviors related to switching between tobacco products.

In a randomized controlled ST intervention study of 1,248 college baseball athletes, [Gansky et al. \(2005\)](#) found that 4 percent of baseline exclusive ST users reported that they had stopped using ST at the 1-year follow-up assessment, but had smoked at least one cigarette in the past 30 days. Of baseline dual users, 14 percent reported that they had quit ST use, but continued to smoke at follow-up.

Of a sample of 4,886 adult males, [Wetter et al. \(2002\)](#) reported that baseline adult dual users used less ST and smoked less than baseline exclusive ST users and smokers, respectively, and were more likely to switch tobacco use, with 17% switching to ST exclusively and 27% to smoking exclusively at the 4-year follow-up assessment; 11.3% reported quitting all tobacco. Baseline ST users were more likely to continue using ST exclusively (76.6%) or quit tobacco completely (20.1%) rather than switching to cigarettes (0.9%) or to dual use (2.5%). Baseline smokers showed a pattern similar to that of ST users, with the majority remaining exclusive smokers (79.7%) or quitting (15.7%) and with a small proportion switching to ST (1.4%) or dual use (3.2%). While ST users were more likely to be abstinent than dual users, the study did not evaluate if there was a statistically significant difference in switching behavior between ST users, smokers, and dual users.

#### **7.5.2-1.2.6. Summary**

Regarding switching behaviors, the literature is mixed. Tobacco switching behaviors in exclusive users appear to be rather infrequent (< 4 percent; [Henley et al., 2007](#); [Wetter et al., 2002](#); [S.-H. Zhu et al., 2009](#)), but when switching does occur, it is more likely to be from ST or dual use to cigarettes [S.-H. Zhu et al. \(2009\)](#). While there is evidence that a proportion of ST users may switch to cigarettes when they cannot or do not want to use ST, ST may also serve as a viable quitting method in some cigarette smokers. Therefore, there is little overall evidence to support switching to cigarettes as being the predominant outcome of ST use. [Table 7.5.2-1-1](#) presents a summary of the publications identified that assessed switching behaviors.



**Table 7.5.2-1-1: Literature Evaluating Tobacco Product Switching Behavior**

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
<b>Longitudinal Studies</b>					
(Henley et al., 2007)	Tobacco-related disease mortality among men who switched from cigarettes to spit tobacco	Longitudinal. Cancer Prevention Study II (1982; 1992/93)  N = 116,395 adult males (N = 4,443 switchers; N = 111,952 cigarette smokers who quit tobacco entirely) (U.S.)	1982 questionnaire: Use of cigarettes, cigars, pipes, chewing tobacco, snuff  1992-3 questionnaire: current smoking	Current smoking in 1992-93 was low: 1.4% for quitters of all tobacco and 3.0% of switchers.	<i>Strengths:</i> Longitudinal Large sample size Prospective design  <i>Limitations:</i> Potential misclassification of tobacco user status Self-report - recall bias
(O’Hegarty et al., 2012)	Are adolescent cigarette smokers who use smokeless tobacco more likely to continue smoking in the future than cigarette-only smokers: results from waves I and II of the adolescent health survey	Longitudinal. National Longitudinal Study of Adolescent Health (Add Health) surveys. Self-administered surveys and in-home interviews  N = 3,284 current smokers at Wave I who were interviewed at Wave II (U.S.)	Experience with cigarettes, ST, and alcohol  Cigarette and ST use	Proportions still smoking at Wave II were similar between cigarette-only users and dual users (78.4% vs. 73.6%).  Unadjusted analysis: Among dual users at Wave I, 37% continued both at Wave II, while 36.6% continued with cigarettes only and 17.9% quit both products. In contrast, for cigarette-only users at Wave I, majority remained exclusive smokers at Wave II (73.4%), while 5% switched to dual use and 1.6% had switched to ST only and 20.0% had quit at Wave II.  Adjusted analysis: Dual users less likely to be smoking than exclusive smokers (OR = 0.71; 95% CI: 0.52-0.98).	<i>Strengths:</i> Longitudinal  <i>Limitations:</i> Biased sampling due to passive consent procedure Short follow-up period
(Tomar, 2003)	Is use of smokeless tobacco a risk factor for cigarette smoking? The U.S. Experience	Longitudinal study. Data were from the 1989 Teenage Attitudes and Practices Survey (TAPS-I) and its 1993 follow-up (TAPS-II). TAPS-I sampling consisted of all teenagers aged 12-18 years on November 1, 1989, who resided in households. Data from 3,996 participants were analyzed.	Participants were asked whether they had ever tried chewing tobacco and snuff, whether they ever considered themselves regular users of these products, and whether they currently were regular users of ST.	There were increases in the prevalence of ST use among participants who used them regularly, current users, former users, and those who used but never regularly from 1989 until 1993 (6.1% to 11.9%, 2.7% to 5.7%, 3.3% to 6.1%, and 23.9% to 30.4%, respectively). The percentage of ST users that initiated cigarette smoking was 23.9% among regular ST users, 14.8% among nonregular ST users, and 7.6% among nonusers of ST. The rates of ST use initiation (current regular use and use within preceding 30 days were 2.4% and 5.1%, respectively for current smokers and 1.5% and 3.9% for never smokers.	Limitations: (1) All data on smoking and ST use were based on self-reports; (2) the study used a definition of ST use that relied on participants’ self-characterization of regular use; and (3) bias might have been introduced because of the differential response rates between tobacco users and nonusers.

(S.-H. Zhu et al., 2009)	Quitting cigarettes completely or switching to smokeless: Do U.S. data replicate the Swedish results?	Longitudinal study (1-year follow-up) using data from TUS-CPS 2002 (2001-2003)  N = 15,056 adults (U.S.)	Tobacco users grouped into cigarette smokers only, ST only, dual users  Nonsmokers are grouped into never smokers and former smokers	<p>Male ST only users: 59.4% continued exclusive use; 3.9% switched to cigarettes; 1.8% became dual users; 35.0% quit ST and used no cigarettes.</p> <p>Male dual users: 45% continued dual use; 37.0% continued smoking, but quit ST; 4.9% continued ST, but quit smoking; 13.1% quit both.</p> <p>Quitting one form of tobacco and switching to another was infrequent. If there was a switch, it was more likely to be from ST to cigarettes than vice versa (3.9% vs. 0.3%).</p> <p>Male switchers from cigarettes only to ST only (0.3%), and to dual use (2.2%).</p> <p>Male switchers from ST only to cigarettes only (3.9%), and to dual use (1.8%).</p> <p>Male switching from dual use to cigarettes only (37.0%), and ST only (4.9%).</p> <p>Female switching from cigarettes only to ST only (0%), and dual use (0.1%).</p> <p>Female switching from ST only to cigarettes only (3.2%), and dual use (0).</p> <p>Female switching from dual use to cigarettes only (71.6%) to ST only (0%) (but only N=5 of them).</p> <p>No discernible association between ST use and population smoking cessation rates.</p> <p>Few male smokers stopped smoking and switched to ST and few former smokers turned to ST. If anything, it was more likely for ST users to switch to cigarettes.</p> <p>Men's smoking cessation rate was no higher than women's (11.7% vs. 12.4%), even though men were much more likely to use ST.</p>	<p><i>Strengths:</i>  Longitudinal  Nationally representative sample</p>
<b><i>Cross-Sectional Studies</i></b>					

(R. G. Boyle et al., 1998)	Use of smokeless tobacco by young adult females	Cross-sectional. Questionnaire and brief interview.  N = 20 ST-using women (upper Midwest)	Cotinine (tested initiation and pattern of ST use, quit attempts, and smoking history)	25% switched to ST to help quit smoking.	<p><i>Strengths:</i></p> <p>Sample of under-represented population (females)</p> <p><i>Limitations:</i></p> <p>Small sample size  Self-report - recall bias  Limited geographical generalizability</p>
(Chakravorty & Chakravorty, 1997)	Cessation related perceptions and behavior of former and current smokeless tobacco users	Cross-sectional. Telephone interview  N = 950 college students (Illinois)	<p>Tobacco-use history</p> <p>Current ST cessation related perceptions</p> <p>"Readiness to change" measure to assess readiness to quit ST</p>	<p>24% of former ST users reported they smoked cigarettes as an aid to quitting ST, while only 6% of ex-smokers said they used chewing or dipping tobacco to help quit smoking cigarettes (<math>p &lt; 0.01</math>).</p> <p>Former ST users were significantly more likely to report current cigarette smoking than former smokers were to report using ST, 12% vs. 0.01% (<math>p &lt; 0.01</math>).</p> <p>Some former ST users smoked cigarettes to help them quit ST.</p>	<p><i>Limitations:</i></p> <p>Cross-sectional  Limited geographical generalizability</p>



(Cohen-Smith & Severson, 1999)	A comparison of male and female smokeless tobacco use	Cross-sectional. Telephone and in person interviews  N = 51 female ST users N = 59 male ST users (Pacific Northwest)	Reasons for use of ST	<p>The primary sex difference was found in the reported use of ST as an alternative to smoking, which ranked second among women's reasons for continuing ST use (17.6%), and next to last among men's reasons (5.1%).</p> <p>51.7% of women used ST in place of smoking while quitting vs. 58.8% of men.</p> <p>Most participants were current smokers or ex-smokers (98% of women and 89.8% of men).</p> <p>When asked what they liked about ST, 33.3% of women and 28.8% of men reported using ST as an alternative to smoking.</p> <p>Association between ST and cigarettes was particularly pronounced with female participants.</p> <p>Unclear whether use of cigarettes functions as a stepping stone toward ST use or conversely, if women who use ST regularly and are addicted to nicotine may be more likely to try cigarettes as a more acceptable form of tobacco use, or as a substitute when ST is unavailable.</p>	<p><i>Strengths:</i> Structured interview</p> <p><i>Limitations:</i> Small sample Self-report - recall bias Lack of matched samples between sexes Limited demographic and geographic generalizability</p>
(D. Hatsukami et al., 1999)	Characteristics of smokeless tobacco users seeking treatment	Cross-sectional. Questionnaire for those enrolled in ST cessation treatment study  N = 402 ST users (Minnesota)	Tobacco use history, including amount, duration, and pattern of ST use, use of other tobacco products	<p>Use of ST as aid to quitting smoking: 25.9% ever smokers 55.3% ever-regular cigarette smokers</p> <p>Use of cigarettes as aid to quitting ST: 14.0% ever smokers 24.4% ever-regular cigarette smokers.</p>	<p><i>Limitations:</i> Cross-sectional Results biased because ST users who were regular smokers (more than 20 cigarettes per month) were excluded</p>

(Brad Rodu & Phillips, 2008)	Switching to smokeless tobacco as a smoking cessation method: evidence from the 2000 National Health Interview Survey	Cross-sectional. 2000 National Health Interview Survey  N = 2,180 smokers attempting to quit N = 3,548 former smokers (U.S.)	Quit attempts	<p>73% of switchers to ST in most recent quit attempt were successful, i.e., were former smokers at the time of the survey.</p> <p>54% of switchers did not use any tobacco product at time of survey, suggesting that switching to ST is not incompatible with goal of achieving complete nicotine and tobacco abstinence.</p> <p>Switching to ST resulted in over twice the proportion of former smokers (73%) than the patch (35%), gum (34%), inhaler (28%) or nasal spray (0%).</p> <p>15% of switchers gradually decreased number of cigarettes smoked, which was higher than for those using bupropion (3%) or patch (4%) as an aid.</p> <p>Of the 261,000 men who switched to ST and became former smokers, 120,000 (46%) were current ST users at time of survey, and the authors indicate that the switch may be permanent for some.</p> <p>“only 42,000 women switched to ST in their most recent quit attempt, and only 38% of them (16,000) were former smokers.”</p>	<p><i>Strengths:</i> Nationally representative</p> <p><i>Limitations</i> Self-report - recall bias Failed attempts not captured</p>
(Tomar, 2002)	Snuff use and smoking in U.S. men — Implications for harm reduction	Cross-sectional. Personal household interviews  N = 13,865 males age 18 or older (U.S.)	Tobacco use history  Quit attempts	<p>U.S. men were more likely to be former snuff users who currently smoked (2.5%; 95% CI: 2.2-2.8) than to be former smokers who currently used snuff (0.9%; 95% CI: 0.7-1.1). Prevalence of current dual use was 1.1% (95% CI: 0.9-1.3).</p> <p>Male smokers who used snuff only on some days were more likely than those who never used snuff to have tried to quit smoking in the preceding 12 months (OR = 1.68; 95% CI: 1.03-2.72).</p> <p>Smokers who were former or daily snuff users did not differ from never users in their likelihood of reporting an attempt to quit smoking.</p>	<p><i>Strengths:</i> Large sample Nationally representative of males</p> <p><i>Limitations:</i> Sequence of product use not known Age at initiation of ST unknown Self-report - recall bias Frequency/intensity of ST use not captured Reasons for switching not captured</p>

<b>Clinical Studies</b>					
(Gansky et al., 2005)	Cluster-randomized controlled trial of an athletic trainer-directed spit (smokeless) tobacco intervention for collegiate baseball athletes: results after 1 year	Stratified, cluster-randomized controlled trial with 1-year follow-up  n = 1,248 male collegiate baseball players (California)	Alcohol and tobacco use history  Current tobacco use status  Patterns of use	Of the 431 exclusive ST users at baseline, 18 (4%) reported at follow-up that they had stopped ST use, but had smoked at least 1 cigarette in the previous 30 days.  Of the 206 baseline ST users who also smoked cigarettes, 29 (14%) reported at follow-up that they quit ST use but continued to smoke.	<i>Strengths:</i> Longitudinal Randomized  <i>Limitations:</i> Limited geographical generalizability Small number of nicotine-dependent ST users (11%)
(Wetter et al., 2002)	Concomitant use of cigarettes and smokeless tobacco: Prevalence, correlates, and predictors of tobacco cessation	Randomized, matched-pair design cancer prevention trial  N = 4,886 males (Southeastern U.S.)	Baseline tobacco and ST use status  Tobacco consumption  Smoking-related measures  ST-related measures (quit attempts, confidence in quitting in next 6 months, stage of change)  Abstinence status	Vast majority of baseline smokers and ST users (77%-80%) remained exclusive users of either ST or cigarettes.  Only about 3% became concomitant users and only about 1% switched tobacco products (i.e., ST to cigarettes or cigarettes to ST).  Less than half (44%) of the baseline concomitant users were still using both ST and cigarettes 4 years later, while 17% had switched exclusively to ST and 27% had switched exclusively to cigarettes.	<i>Strengths:</i> Large sample size Randomized  <i>Limitations:</i> Cross-sectional Self-report - recall bias Working Well Trial was not specifically designed to address the specific questions of dual use or gateway.

### **7.5.2-1.3.The Likelihood that Consumers Will Use the Product in Conjunction with Other Tobacco Products**

#### **7.5.2-1.3.1. Overview**

The current analysis of the potential use of ST in conjunction with other tobacco products is centered on the term “dual use.” The term *dual use* has been used to describe tobacco users who smoke cigarettes and, interchangeably, also who consume an alternate tobacco product. The term *dual use* is not intended to describe consumers who use multiple products at the same time (e.g., smoke cigarettes while using ST), but rather describes those consumers who alternate between products at various times for a variety of reasons. While the term could apply to those who consume any other noncigarette tobacco product (e.g., cigars, hookahs), the literature review was limited to studies that evaluated dual use of ST and cigarettes, since this type of dual use may confer the greatest health risks and smoking represents the predominant form of tobacco use in the U.S. There also exists limited information on concurrent use of ST with other tobacco products because other tobacco products are used less frequently/more intermittently than cigarettes and have a lower prevalence of use. Thus, this section reports the prevalence, correlates, and use behaviors of dual use of ST with cigarette smoking.

When reviewing the literature on the prevalence and behavioral characteristics of dual use, the biggest uncertainty was the variation and lack of consistency in defining dual use. Frequency of use of either product, use of specific ST (e.g., chewing tobacco, snuff), and the nuances of alternating product usage were also not well defined or captured in many articles. For example, a regular ST user who smokes occasionally is characterized as a dual user, and a regular smoker who uses ST occasionally is also characterized as a dual user. In some instances, smokers use ST on occasion, while in other cases ST users smoke an occasional cigarette. A few consumers report daily use of both products, while others report less frequent (weekly or monthly) occurrence. Some consumers, especially adolescents, are most likely experimenting with multiple tobacco products (e.g., (Creath, Wright, & Wisniewski, 1992; Rath, Villanti, Abrams, & Vallone, 2012) ) and have not reached a steady state of tobacco use, while others may be using alternative tobacco products to stop smoking (e.g., (Cohen-Smith & Severson, 1999); see also Section 7.5.2-1.4). Another limitation of the available literature is that many of the publications are older, having been published in the 1980s and 1990s. While these are provided for completeness, the focus is primarily on more recent publications (i.e., 2000 onward) because these are considered more reflective of current trends in dual use.

Based on the available literature, dual use of ST and cigarettes exhibits a significantly lower prevalence than with cigarette smoking (past month cigarette use: 20.8%, 2014 National Survey on Drug Use and Health [NSDUH] (Center for Behavioral Health Statistics and Quality, 2015)), with an estimated prevalence of approximately 5.0% (range: 0.9% to 15.0%, n = 17 studies) in adolescents and 3.1% (range: 0%-10.0%, n = 17 studies) in adults. Whereas exclusive cigarette smoking has declined since the early 2000s, the prevalence of dual use has remained relatively stable (e.g., (Arrazola, Kuiper, & Dube, 2014) [adolescents], but see (Fix et al., 2014) [adults]). It was also observed that there is a higher proportion of ST

users who smoke cigarettes than there is for cigarette smokers who use ST (e.g., (Agaku, Ayo-Yusuf, Vardavas, & Connolly, 2014; Elizabeth A. Mumford, Levy, Gitchell, & Blackman, 2005; Herbert H. Severson, Forrester, & Biglan, 2007)), although the number of ST users is significantly lower than that for cigarette smokers. This latter observation further underscores the importance of defining dual use.

Overall, the current literature shows that many demographic characteristics of dual users are similar to those of exclusive ST users, including younger age, white, and male (e.g., (McClave-Regan & Berkowitz, 2011; Brad Rodu & Cole, 2009; Wetter et al., 2002; S.-H. Zhu et al., 2009)). With respect to use behaviors, data suggest that dual users smoke fewer cigarettes than exclusive smokers (e.g., (Brad Rodu & Cole, 2009; Wetter et al., 2002)), supporting the notion that one tobacco product serves as a substitute for another product in some users. There is also evidence suggesting that dual users may exhibit more signs of nicotine dependence than those who consume only a single product (e.g., (Apelberg et al., 2014; Kram et al., 2014)). With respect to dual use as a method of smoking cessation, the data suggest that, compared with exclusive smokers, dual users are less likely to stop all tobacco use over time, but they are more likely to reduce smoking intensity (e.g., (Frost-Pineda, Appleton, Fisher, Fox, & Gaworski, 2010)).

#### **7.5.2-1.3.2. Literature Review Results**

To examine dual use behavior, literature was collected that met the initial search criteria identifying investigational studies with U.S. tobacco consumer cohorts. Many of the studies appearing in the literature included other oral tobacco products beyond the ST product subject to this MRTPA. Publications were included in the review when information on individual product types was included within a study. Studies exclusive of U.S. products were not included in the review.

Participants in these studies included mainly adolescents, college students, and adults. The number of participants evaluated in these studies ranged from as few as 20 (Jon O. Ebbert, Croghan, North, & Schroeder, 2010) to nationally representative weighted samples (e.g., (Saunders & Geletko, 2012) or (Fix et al., 2014)). Most published studies were cross-sectional in nature and included small to moderate sample sizes. The most relevant information is from the longitudinal studies and those studies that utilize larger national health surveys.

#### **7.5.2-1.3.3. Prevalence of Dual Use of ST and Cigarettes**

There were 92 publications which reported on the prevalence of dual use of ST and cigarette smoking in adolescent, college age, and adult samples in the U.S. The information related to dual use was generally limited to prevalence measurements only. Some of the studies were specifically designed to investigate the prevalence of dual use among a certain demographic, while in other cases, dual use prevalence data were extracted from the tobacco use data described in the study. In many cases, the prevalence estimates are based on male participants only since the rate of ST use in females is extremely low.

A considerable degree of variation exists in the reported prevalence of dual use of ST and cigarettes among the identified publications, which is consistent with the variability of

defining dual use between the studies, limitation with bias and self-reporting, and demographic differences represented in the data.

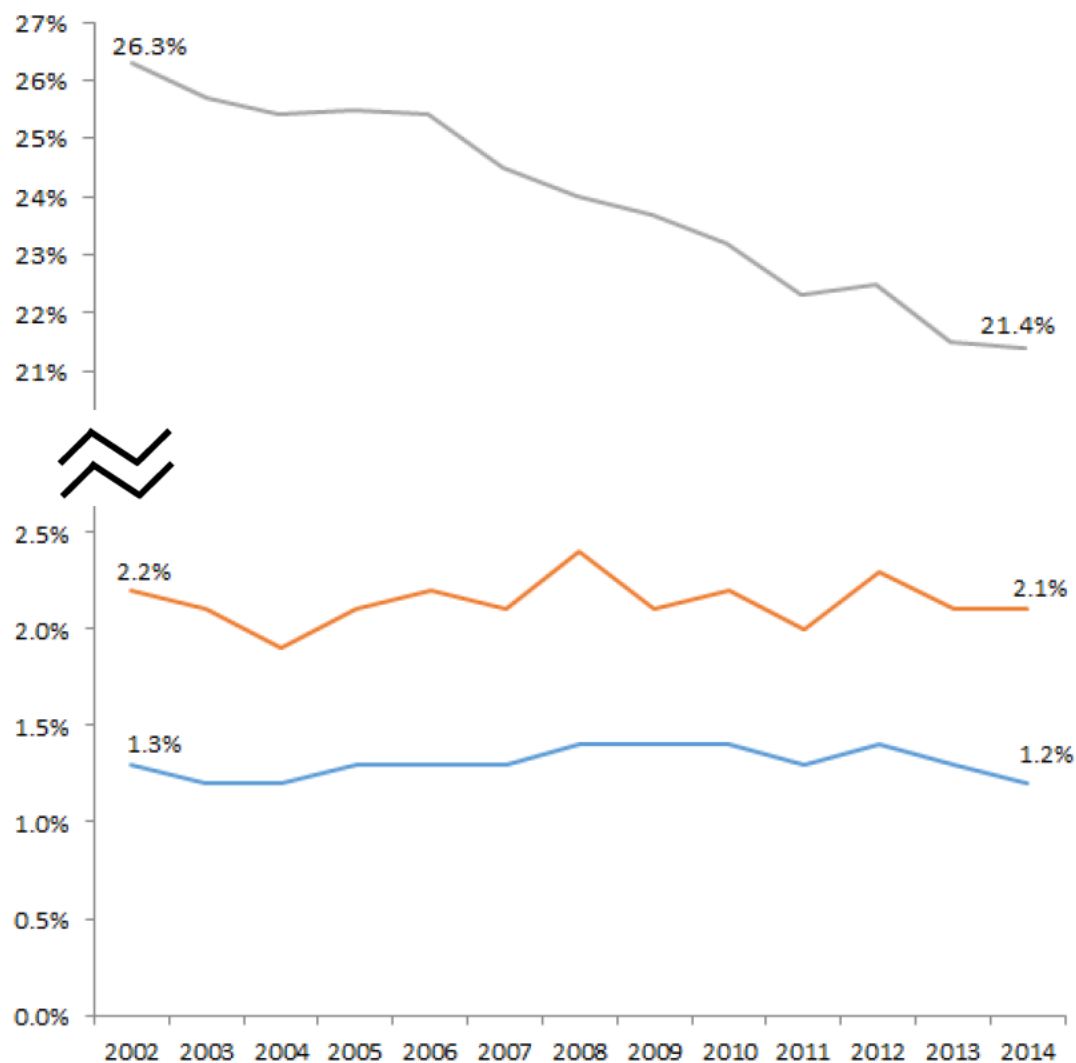
In general, studies in adolescents reported an overall average prevalence of dual use of 5.0% (range: 0.9%-15.0%; n = 17 studies). In adults, the average prevalence of dual use was 3.1% (range: 0%-10.0%; n = 17 studies). [Klesges et al. \(2011\)](#) reported on the effect of dual use definitions and demonstrated that estimates of prevalence could vary up to 50-fold when considering dual use (all products; 0.5%-25.3%), and approximately four-fold for dual use of ST and cigarettes (2.0%-9.7%). In that study, prevalence of daily ST and cigarette dual use among adults was estimated to be 3.3%, which is consistent with the average reported estimates in the general population. Certain demographics report higher mean (range) concurrent use of ST and cigarettes than the general adult population, for example, Alaska natives/Native Americans (5.5% [3.2%-8.7%]; n = 7 studies), military personnel (12.6% [7.9%-20.0%]; n = 4 studies), and firefighters (7.4% [2.6%-12.2%]; n = 2 studies).

Among those who report sustained ST use, the prevalence of concurrent cigarette smoking is typically over 30% in adolescents (mean [range], 47.3% [13.5%-74.3%]; n = 7 studies), college students (35.1% [10%-67%]; n = 3 studies), and adults (24.3% [5%-60%]; n = 8 studies). In contrast, ST use in cigarette smokers is notably less (< 20% on average; adolescents: 18.4%, college students: 9.5%; adults: 12.9%).

To illustrate the status of dual use in the U.S., the reported incidences for past 30-day ST use only, past 30-day cigarette smoking only, and past 30-day ST use and cigarette smoking from the NSDUH (2002-2014) are presented in [Figure 7.5.2-1-1](#).

The prevalence of past 30-day ST use remained fairly constant for more than a decade, averaging approximately 2.1% (range: 1.9%-2.4%). These nationally representative estimates for rates of past 30-day ST use are in line with many of the prevalence estimates reported in the literature reviewed. Approximately 30%-40% of those who reported past 30-day use of ST also reported past 30-day cigarette smoking, which is consistent across adolescent, college student, and adult ST using populations. Again, these prevalence estimates are consistent with those reported in various publications. One caveat regarding the survey numbers reported is the lack of any relevant endpoint to assess sustained behavior of either tobacco use activity beyond the 30 days. Overall, these nationally representative data provide a reasonably consistent illustration of the trends in self-reported dual use among U.S. tobacco users over time. It appears that, over the past decade, the trends in dual use of cigarettes and ST have been relatively consistent.

**Figure 7.5.2-1-1: Prevalence of Concurrent ST Use and Cigarette Smoking Using Data from the National Household Survey on Drug Abuse (1988 to 1998) and the National Survey on Drug Use and Health (1999-2012)**



Source and notes: ALCS analysis of National Survey on Drug Use and Health public access files. Smokeless tobacco measured as reported past 30-day use of snuff or chewing tobacco. Use of other tobacco products not included in the analyses or reflected in the Figure.

Table 7.5.2-1-2 presents a summary of the literature reporting on the prevalence of dual use of ST and cigarette smoking in adolescent, college age, and adult samples in the U.S.

**Table 7.5.2-1-2: Literature Evaluating Prevalence of Dual Use of Moist Smokeless Tobacco and Cigarette Smoking**

Author	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
<b>Adolescents</b>					
(Agaku, Ayo-Yusuf, Vardavas, Alpert, & Connolly, 2013)	Use of conventional and novel smokeless tobacco products among U.S. adolescents	Cross-sectional. Survey (2011 NYTS)  N = 18,866 middle and high school students (U.S.)	Prevalence of use in past 30 days of smokeless and combustible and other tobacco products  “Any” ST included dissolvables and snus, and conventional ST (snuff, chewing or dipping tobacco)	<i>Proportion (%)</i> Any ST product use: 5.6% Cigarettes: 13.0% Dual use: 4.0% Concurrent use of combustible products in any ST users: 72.1% Concurrent use of combustible products in conventional ST users: 65.2%	<i>Strengths:</i> Nationally representative Large sample size  <i>Limitations:</i> Cross-sectional Self-report - recall bias
(Agaku et al., 2014)	Predictors and patterns of cigarette and smokeless tobacco use among adolescents in 32 countries, 2007-2011	Analysis of cross-sectional surveys (2007-2008 Global Youth Tobacco Surveys and the 2011 NYTS)  Students from 32 countries (age: 13-15 years) (estimated N = 8,584 U.S. students)	Prevalence of current smoking, ST use and dual use (past 30 days)	<i>Proportion (%) – U.S. only</i> ST use: 3.4% Smoking: 8.0% Dual use: 1.7% Smokers who use ST: 21.3% ST users who smoke: 51.9%  Dual use is more common in high income countries like the U.S. More than half of all current ST users in the 10 European countries surveyed as well as in the U.S. concurrently smoked cigarettes.	<i>Strengths:</i> Global assessment Large sample sizes  <i>Limitations:</i> Cross-sectional Self-report Product generalizability



Author	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
(Arrazola et al., 2014)	Patterns of current use of tobacco products among U.S. high school students for 2000-2012--findings from the National Youth Tobacco Survey	Cross-sectional. Survey (2000-2012 NYTS)  N = 9,198-18,219 high school students depending on year of survey. (U.S.)	Prevalence, patterns and trends of current tobacco use (past 30 days)	<i>Proportion (%)</i>			<i>Strengths:</i> Large sample size Nationally representative  <i>Limitations:</i> Limited generalizability to other age groups Self-report Sample handling Frequency and intensity of use not evaluated
				Cigarettes: 2000: 14.0% 2002: 12.3% 2004: 11.3% 2006: 9.3% 2009: 8.1% 2011: 6.3% 2012: 4.7%	ST use: 1.4% 1.4% 1.3% 1.5% 1.6% 2.2% 1.6%	Dual use: 1.2% 1.2% 0.9% 1.0% 1.3% 1.5% 1.0%	
				From 2000-2012, significant decline in current use of any tobacco (33.6% to 20.4%, p < 0.05) and cigarette smoking, but no significant change in prevalence of dual use. Nearly 1 in 10 students were polytobacco users.			
(Ary, Lichtenstein, Severson, Weissman, & Seeley, 1989)	An in depth analysis of male adolescent smokeless tobacco users; interviews with users and their fathers	Longitudinal. Survey using in-person and telephone interviews  N = 101 male adolescent experimental (< 10 lifetime uses) ST users N = 90 male adolescent current (> 10 lifetime use and past-month use) ST users (Oregon)	Rate, pattern of use over 6-month period (last week and last 24 hours)	Use of cigarettes by current ST users: > 1 cigarette: 83% Past week: 22% Daily: 12.2%  Current ST use associated with greater likelihood of using cigarettes and ST on same day, as compared with that for experimental users (45.8% vs. 4.8%, p < 0.0001).			<i>Strengths:</i> In-depth interviews  <i>Limitations:</i> Small sample size Low response rate Limited geographical generalizability

Author	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(C. L. Backinger, Bruerd, Kinney, & Szpunar, 1993)	Knowledge, intent to use, and use of smokeless tobacco among sixth grade schoolchildren in six selected U S sites.	Cross-sectional. Questionnaire  N = 781 Alaska native/American Indian and non-Alaska native/American Indian 6th grade students (Georgia, Massachusetts, Texas, Alaska, Montana, Wyoming, Arizona, New Mexico)	Use of ST and cigarettes	Of those who tried ST, 61.3% from state sites and 59.9% from Indian Health Service sites reported trying cigarettes.  One student from state sites and 12 students from IHS sites reported dual use of ST and cigarettes	<i>Strengths:</i> Moderate sample size  <i>Limitations:</i> Cross-sectional Self-report – recall bias Limited generalizability
(Bombard, Rock, Pederson, & Asman, 2008)	Monitoring polytobacco use among adolescents: do cigarette smokers use other forms of tobacco?	Cross-sectional. Surveys (2002 and 2004 NYTS)  N = 51,730 students (729 excluded from concurrent tobacco use estimates) (U.S.)	Prevalence of smoking and other tobacco product use	Cigarettes and 1 additional tobacco product: 26.4%; Of those dual product users, 17.1% used ST  Dual product users using cigarettes and ST: Female: 8.0% Male: 23.2% Middle school: 16.3% High school: 17.4%  Of those reporting use of 1 tobacco product with smoking, most used cigars, followed by ST. Polytobacco use was more prevalent in males than in females.	<i>Strengths:</i> Large sample size Nationally representative  <i>Limitations:</i> Cross-sectional
(R. G. Boyle, Claxton, & Forster, 1997)	The role of social influences and tobacco availability on adolescent smokeless tobacco use.	Cross-sectional. Survey  N = 2,924 adolescent male middle and high school students (Minnesota)	Prevalence and correlates of ST use (past 24 hours and 7 days)  Cigarette use (past month)	ST use: 10% Dual use: 64.3% of ST users  Past week ST use: Smoking (past month): OR: 2.87; 95% CI: 2.05-4.03  Majority of ST users reported concurrent use of cigarettes in past month.	<i>Strengths:</i> Mixed-model logistic regression  <i>Limitations:</i> Cross-sectional Limited geographical/ demographic generalizability

Author	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Camenga et al., 2014)	Alternate tobacco product and drug use among adolescents who use electronic cigarettes, cigarettes only, and never smokers	Cross-sectional. Survey (2010/2011)  N = 3,102 high school students (Connecticut, New York)	Self-reported use (past 30 days)	Smokers who also use ST: 13.7% Never smokers who use ST: 0.8%  Alternative tobacco product use was more likely in current cigarette smokers than in never smokers.	<i>Limitations:</i> Cross-sectional Small sample size Self-report Limited geographical/ demographic generalizability
(Chisick, Lee, Raker, & Williams, 1992)	A profile of tobacco use among teenage dependents	Cross-sectional. Survey questionnaire (1989)  N = 2,241 middle and high school students at 2 Army posts (Kentucky)	Self-reported trial and use	Tobacco tried: Smoking only: 27.7% ST only: 3.2% Both: 13.2%  <u>Age (e.g., grade, %): 6 9 12</u> Smoking only: 16.7% 29.4% 34.7% ST only: 3.1% 3.6% 7.1% Both: 7.3% 14.7% 19.4%	<i>Limitations:</i> Cross-sectional Self-report Limited geographical/ demographic generalizability
(Colborn, Cummings, & Michalek, 1989)	Correlates of adolescents' use of smokeless tobacco	Cross-sectional. Survey questionnaire  N = 568 adolescents from 5 public schools (New York)	Past and current tobacco use practices  Ever tried Current use (past week)	Ever tried: Overall: Boys Girls Smoking: 72% 75% ST use: 69% 18%  Boys (ST users vs. non-ST users) Tried smoking: 86% vs. 68% (p = 0.02) Current smoking: 25% vs. 23% (NS)  Current use of cigarettes was not related to current use of ST.  The majority of male students surveyed reported experimentation with ST and cigarettes, however, few regular ST users were current smokers (as stated by the author), suggesting adolescent males may experiment with different forms of tobacco, but may choose one preferred type.	<i>Limitations:</i> Cross-sectional Self-report – recall bias Limited generalizability Regional and age differences cannot be separated due to sampling method

Author	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Danaher et al., 2013)	Randomized controlled trial of MyLastDip: a Web-based smokeless tobacco cessation program for chewers ages 14-25	Randomized controlled trial (MyLastDip web-based cessation intervention program)  N = 1,716 treatment-seeking adolescent and young adult ST users (U.S. [97.5%], Canada)	Baseline ST use and smoking characteristics of participants  Predictors of cessation	Current smoking in ST users: 13.5% Lifetime smoking ( $\geq 100$ cigarettes) in ST users: 43.0%	<i>Strengths:</i> Large sample size Prospective evaluation Geographically diverse Real-world assessment of intervention Longitudinal assessment Good retention (71% at 6 months)  <i>Limitations</i> Self-report – recall bias
(Daughety, Levy, Ferguson, Pomrehn, & Becker, 1994)	Surveying smokeless tobacco use, oral lesions and cessation among high school boys	Cross-sectional. Survey  N = 821 11th and 12th grade boys (eastern Iowa)	ST and cigarette use	Approximately 22% of experienced ST users (>20 times, n = 183) reported current (weekly or more) use of ST, alcohol, and cigarettes.	<i>Limitations:</i> Cross-sectional Self-report Limited geographic/ demographic generalizability
(de Moor et al., 1994)	Patterns and correlates of smoking and smokeless tobacco use among continuation high school students.	Cross-sectional. Survey  N = 619 students attending continuation high schools (California)	ST and cigarette use	Smoking: Tried: 81.7% $\geq 1/\text{month}$ : 55.1% > 1/week: 50.4% Almost/daily: 43.9%  ST use: Tried: 22.3% $\geq 1/\text{month}$ : 5.7% $\geq 1/\text{week}$ : 2.9% Almost/daily: 1.8%  Monthly ST use more common in weekly smokers vs. nonsmokers (8.3% vs. 2.9%) (p < 0.01).  Weekly smoking more common among ST users vs. non-ST users (74.3% vs. 49.0%) (p < 0.01).	<i>Limitations:</i> Cross-sectional Limited sampling due to absenteeism, time limitations Small sample of ST users Lack of generalizability Self-report – recall bias
(Dent et al., 1987)	Adolescent smokeless	Longitudinal.	Ever use of cigarettes and	Trial (proportion): Grade 8 Grade 9	<i>Strengths:</i>

Author	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
	tobacco incidence: relations with other drugs and psychosocial variables	School-based survey (1- year follow-up)  N = 2,714 middle school students (California)	ST  Lifetime number of cigarettes  Current number of cigarettes  Predictors of ST use onset	ST: 19% 27% Cigarettes: 63% 74%  ST onset related to higher levels of cigarette smoking and lower quit rates.	Longitudinal Multivariate regression  <i>Limitations:</i> Limited geographical/ demographic generalizability ST use variables not captured Self-report – recall bias
(Erickson, Lenk, & Forster, 2014)	Latent classes of young adults based on use of multiple types of tobacco and nicotine products	Latent class analysis of prospective cohort study (2000-2008) N = 4,826 young adults with the initial age of 12- 16 y (Midwestern U.S.)	Past 30-day smoking  Ever use of ST, including chewing tobacco/snuff/dip, snus	Ever smoking: 59% Ever ST use: 19% chew/snuff 15% snus  Latent class analysis: Approximately 7% characterized as polytobacco users (vs. 10% ST user and 13% cigarette smoker classes).  ST user class also reported modest amount of current cigarette use.	<i>Strengths:</i> Longitudinal (overall) Statistical analysis  <i>Limitations:</i> Cross-sectional analysis Limited geographical generalizability Attrition (31%) may underestimate prevalence of tobacco/nicotine use classes Limited details on use of noncigarette products Self-report – recall bias
(Everett, Malarcher, Sharp, Husten, & Giovino, 2000)	Relationship between cigarette, smokeless tobacco, and cigar use, and other health risk behaviors among U.S. high school students	Cross-sectional. Survey (1997 Youth Risk Behavior Survey)  N = 16,262 adolescents (U.S.)	Past 30-day use of cigarettes, ST, cigars  Current use: ≥1 day in past 30 days	Current use: Single tobacco product: 24% Cigarettes only: 17.8% ST only: 1.8% Cigars: 4.4%  ≥ 1 tobacco product: 19.5% Cigarettes and ST: 2.1%	<i>Strengths:</i> Large, nationally representative sample  <i>Limitations:</i> Cross-sectional design does not permit causal inference.

Author	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Gansky, Ellison, Kavanagh, Isong, & Walsh, 2009)	Patterns and correlates of spit tobacco use among high school males in rural California	Cross-sectional. Self-administered questionnaire (2000-2004)  N = 4,731 high school males (rural California)	Past 30-day use of tobacco  Patterns of ST use, including frequency and duration of use, age at initiation	Tobacco use (weighted): Cigarettes or cigars 18.5% ST: 9.8% Cigarettes and ST: 5.9%  ST use among smokers: Overall: 32%, OR: 8.55; 95% CI: 6.44-11.4 (ref: nonsmoker)  Smokers 2.5-30 times more likely to use ST than nonsmokers, depending on race/ethnicity.	<i>Limitations:</i> Cross-sectional Self-report – recall bias Low participation
(Gilpin & Pierce, 2003)	Concurrent use of tobacco products by California adolescents	Cross-sectional. Survey (California Tobacco Survey)  N = 6,090 adolescents (California)	Ever and current (past 30-day) use of ST and other tobacco products by smoking experience and known predictors of cigarette use	Ever ST use: Never smokers: 0.5% Noncurrent smokers: 6% Current smokers: 29.2%  Current ST use: Never smokers: 0.05% Noncurrent smokers: 1.0% Current smokers: 6.0%  Over 40% of current established smokers report past month use of another tobacco product (ST, cigars, bidis).	<i>Strengths:</i> Large sample  <i>Limitations:</i> Cross-sectional Self-report – recall bias Limited capture of amount/frequency of use
(Horn, Gao, Dino, & Kamal-Bahl, 2000)	Determinants of youth tobacco use in West Virginia: a comparison of smoking and smokeless tobacco use	Cross-sectional. Self-administered, in-class survey  N = 883 9th grade students (rural West Virginia)	Current use of cigarettes and ST (current = any level of use)  Predictors of tobacco use	Current use: Cigarettes: 20% ST use: 6% Dual use: 10%  Dual use: Males/females: 90%/10%	<i>Limitations:</i> Cross-sectional Self-report Limited demographic and geographic generalizability Limited categories of use

Author	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Kegeles, Burleson, & Miozza, 1989)	Cigarette and smokeless tobacco use among Connecticut adolescents	Cross-sectional. Random sample in-class survey  N = 7,457 7th-12th grade students (Connecticut)	Daily use rates of ST and cigarettes	Cigarette use: 11.6% ST use: 1.9% Cigarette and ST use: 0.9%  0.4% to 1.3% of students were dual users (0.7% to 2.8% in boys), depending on the grade.	<i>Limitations:</i> Cross-sectional Self-report Limited geographical generalizability
(Marty, McDermott, & Williams, 1986)	Patterns of smokeless tobacco use in a population of high school students	Cross-sectional. In-class survey  N = 901 high school students (Arkansas)	Prevalence of ST use and factors associated with initiation and maintenance	Dual use: 28.2% among 170 ST users (5.3% of total sample)	<i>Limitations:</i> Cross-sectional Limited geographical generalizability Level of cigarette use not assessed
(Marty, McDermott, Young, & Guyton, 1986)	Prevalence and psychosocial correlates of dipping and chewing behavior in a group of rural high school students	Cross-sectional. Survey (Marty-Williams Smokeless Tobacco Users inventory)  N = 179 high school students (rural Arkansas)	Prevalence/frequency of ST use behavior and cigarette smoking	ST users: Males: 31.8% (periodic use) Females: 2.3%  Cigarette use (occasional): 27%  Dual use (total sample): 4.5%	<i>Limitations:</i> Cross-sectional Small sample size Limited generalizability Use not well-defined
(Noland et al., 1990)	Use of snuff, chewing tobacco, and cigarettes among adolescents in a tobacco-producing area	Cross-sectional. In-class survey  N = 1,067 7th-12th grade students (Kentucky)	Prevalence and patterns of ST and cigarette use  Salivary cotinine/thiocyanate concentrations	Cigarette use: Grades 7-9 10-12 Rural ST users: 36% 40% Urban/suburban ST users: 47% 63%  Cigarette use among ST users was common, and such crossover use may indicate a dependence on nicotine resulting in seeking out nicotine regardless of tobacco type.	<i>Strengths:</i> Biochemical verification of self-reported tobacco use  <i>Limitations:</i> Cross-sectional

(Rath et al., 2012)	Patterns of tobacco use and dual use in U.S. young adults: the missing link between youth prevention and adult cessation	Longitudinal. Cohort online survey study (Legacy Young Adult Cohort Study)  N = 4,201 young adults (18-34 years) (U.S.)	Trajectories of tobacco use Tobacco use measures: Ever use First product use Past 30-day use Number of cigarettes per day	Ever use: Cigarettes: 51% Cigars: 31% ST: 6%-10%, depending on type  Dual use: Full sample: 7% Current tobacco users: 30%  Dual-use pattern (past 30 days): Cigarettes: 98% Cigars: 23% Little cigars: 26% Dip or snuff: 12% Chewing tobacco: 12% E-cigarettes: 9%  Dual users smoke similar amount of cigarettes per day as exclusive smokers.	<i>Strengths:</i> Large sample Nationally representative  <i>Limitations:</i> Cross-sectional (baseline assessment) Self-report Dual use did not differentiate among noncombustible tobacco products
(Saunders & Geletko, 2012)	Adolescent cigarette smokers' and non-cigarette smokers' use of alternative tobacco products	Reanalysis of cross-sectional surveys (2004, 2006, and 2009 NYTS)  N = > 37 million (weighted) middle and high school students (14-17 years) (U.S.)	Current tobacco use (past 30 days)	Tobacco use: All Smokers Nonsmokers ST: 5.5% 18.0% 2.9% Cigars: 10.6% 38.7% 4.7% Pipes: 3.3% 12.3% 1.4% Bidis: 2.4% 8.9% 1.0% Kreteks: 2.3% 9.9% 0.7%  The authors reported that 1.16 million cigarette smokers were current users of ST (18% of the estimated smoking population).  Current smokers more likely to use any alternative tobacco product.  Male smokers 8 times more likely to use ST than female smokers.	<i>Strengths:</i> Nationally representative sample  <i>Limitations:</i> Cross-sectional Self-report



(Schinke, Gilchrist, Schilling, & Senechal, 1986)	Smoking and smokeless tobacco use among adolescents: trends and intervention results	Longitudinal. Survey study (2 years)  N = 1,281 5th and 6th graders (Washington state)	Tobacco use trends, perceptions and prevention effects	Baseline/2 years: Smoker ST user Smoker: 73% 33% ST user: 67% 54%  Approximately half of ST users intended to smoke, and two-thirds were actually smoking at the 2-year follow-up.	<i>Strengths:</i> Longitudinal  <i>Limitations:</i> Low rates of use at baseline (actual number of students not specified) Small sample size Limited generalizability
(Herbert H. Severson et al., 2007)	Use of smokeless tobacco is a risk factor for cigarette smoking	Longitudinal. Survey (Project SixTeen community intervention; 2-year follow-up, data collected 1994-1999)  N = 2,263 7th and 9th grade male students at baseline (rural Oregon)	Past 30-day ST use Past 30-day cigarette use  Initiation of smoking/ST use, using past 24 hour, past week and past month smoking/ST use coded to weekly smoking/ST use index	Of baseline ST users, at follow-up: Nonsmoking ST user: 26.2% Switch from ST to cigarette: 16.6% Dual use: 40.7%  Of baseline smokers, at follow-up: Non-ST using smoker: 46.8% Switch from cigarette to ST: 3.8% Dual use: 23.8%  Of baseline nonsmokers/non-ST users, at follow-up: Cigarettes: 15.7% ST use: 4.6% Dual use: 8.3%  At follow-up, approximately 18.5% of sample reported dual use.	<i>Strengths:</i> Longitudinal  <i>Limitations:</i> Limited geographic generalizability Did not report dual use at baseline.
(Simon, Sussman, Dent, Burton, & Flay, 1995)	Prospective correlates of exclusive or combined adolescent use of cigarettes and smokeless tobacco: a replication-extension	Longitudinal. Survey (1-year follow-up)  N = 842 7th grade adolescents (southern California)	Prevalence of tobacco product trial  Initiation of use of cigarettes, ST or both products in baseline nontobacco users	Baseline trial: Males Females ST only: 2% < 1% Cigarettes only: 27% 30% Dual use: 7% 1%  Baseline/follow-up (males): ST Cigarettes Dual ST 1% 0% 1% Cigarettes 0% 22% 6% Dual use 0% 0% 7%	<i>Strengths:</i> Longitudinal Biochemical verification <i>Limitations:</i> Small sample size ST users in 7 <sup>th</sup> grade could not be analyzed due to small sample size Regular tobacco use not examined (too low across categories)
(Soneji, Sargent,	Multiple tobacco	Cross-sectional.	Use of 11 tobacco products	Single product use: 54%	<i>Limitations:</i>

& Tanski, 2016)	product use among U.S. adolescents and young adults	Web-based survey (second wave of the Dartmouth Media, Advertising, and Health Study)  N = 927 16–26 year olds (U.S.)	(past 30 days)	Dual product use: 25% Multiple product use: 21%  The authors did not specifically report the actual percentage of dual users of cigarettes and ST in the paper, but one can derive an estimate of ~15% prevalence from visual interpretation of a figure appearing in the paper.	Cross-sectional Self-report - recall bias Frequency/ intensity of use not captured
(M. M. Walsh et al., 2010)	Smokeless tobacco cessation cluster randomized trial with rural high school males: intervention interaction with baseline smoking	Longitudinal. Randomized controlled intervention trial (1-year follow-up)  N = 4,731 male high school students (rural California)	Baseline use of ST and smoking	Baseline: Cigarettes: 13.5% ST (dip or chew): 9.7% Dual use: 5.7%  7.8% of baseline smokers initiated ST use 19.4% of baseline ST users initiated smoking.	<i>Strengths:</i> Longitudinal Randomized controlled trial  <i>Limitations:</i> Self-report Limited geographical generalizability
(M. Walsh et al., 2003)	Spit (smokeless) tobacco intervention for high school athletes: results after 1 year	Randomized controlled intervention trial (1-year follow-up)  N = 1,084 male high school baseball players (rural California)	Baseline prevalence of ST and cigarette use	Current ST use: 28% Of those, 11% (~33 students) reported current smoking	<i>Strengths:</i> Longitudinal Biochemical verification
(Wiener, 2013)	Association of smokeless tobacco use and smoking in adolescents in the United States: an analysis of data from the Youth Risk Behavior Surveillance System survey, 2011	Cross-sectional. Survey (2011 U.S. Youth Risk Behavior Surveillance System)  N = 9,655 9th-12th grade students (U.S.)	ST and cigarette use (past 30-days)	Prevalence: Smoking: 16.8% Dual use: 3.92% Association between ST use and smoking (reference = no ST use): Overall : OR (95% CI): 9.68 (7.72-12.13), p < 0.0001 AOR (95% CI): 3.92 (2.89-5.31), p < 0.0001 In males: AOR (95% CI): 3.73 (2.63-5.30), p < 0.0001 In females: AOR (95% CI): 5.45 (2.16-13.74), p < 0.001 Odds of ST use increased as a function of smoking, and this association held across all races/ethnicities.	<i>Strengths:</i> Large, nationally representative sample  <i>Limitations:</i> Cross-sectional Self-report Potential confusion of what constitutes ST by respondents

**College Students**

(Enofe, Berg, & Nehl, 2014)	Alternative tobacco use among college students: who is at highest risk?.	Cross-sectional. Online survey  N = 24,055 college students (southeastern U.S.)	Cigarette and alternative tobacco product use (past 30-days)	66.9% of chew or snus users also smoked. 9.5% of cigarette users also used chew or snus.	<i>Strengths:</i> Large sample size  <i>Limitations:</i> Cross-sectional Low response rate Limited generalizability to general population
(Foreyt et al., 1993)	Psychological profile of college students who use smokeless tobacco.	Cross-sectional. Survey  N = 1,637 college students (Texas)	Prevalence of cigarette and ST use	Cigarettes ST Dual Females: 32.3% 0.7% 0.2% Males: 22.6% 11.1% 6.1%  Of male ST users, 28.3% reported dual use.	<i>Limitations:</i> Cross-sectional Limited geographical generalizability
(Gray, 1993)	The relationship of cigarette smoking and other substance use among college students	Data from a survey of 863 college students at three Oregon universities were used to assess smoking status, use of ST and use of alcohol, marijuana, and other illicit drugs.	Self-reported use	The authors reported: “Of the 4.6% of those who used smokeless tobacco daily, 10% of them also smoked cigarettes regularly.”	<i>Limitations:</i> Limited geographical generalizability
(Dennis E McChargue, Cohen, & Cook, 2004)	The influence of personality and affect on nicotine dependence among male college students.	Cross-sectional study  N = 137 male college students (Illinois)	Current use of ST and cigarettes (not otherwise defined)	Cigarettes only: 61% (83/137) ST only: 17.5% (24/137) Dual use: 22% (30/137)	<i>Limitations:</i> Cross-sectional Small sample size Limited generalizability
(Miller, Lechner, Meier, Tucker, & Wiener, 2014)	Dual tobacco use among college students: contexts of use, self-perceptions, and attitudes toward quitting	Cross-sectional. Survey (2010)  N = 1,242 college students (southwestern U.S.)	Self-reported tobacco use variables	Cigarettes only: 12.4% ST only: 4.8% Dual use: 4.0%  Males reported higher ST use and dual use than females (9.7% vs. 0.5%, and 7.5% vs. 1.1%, respectively).	<i>Strengths:</i> Multiple variables addressed in larger study of dual use.  <i>Limitations:</i> Cross-sectional Single college; limiting generalizability

<b>Adults</b>					
(Auth & Warheit, 1986)	Smokeless tobacco and concomitant cigarette, pipe, and cigar use among adults in Florida, 1984-1985	Cross-sectional. Field survey (including interview and phone survey)  N = 2,115 adults (Florida)	Current and former tobacco use (measures not further specified)	White males Black males (18-24 y) Cigarettes only: 20.5% 7.7% ST only: 6.0% 0.0% Dual use: 1.2% 15.4%	<i>Limitations:</i> Cross-sectional Limited generalizability Tobacco use frequency/intensity not captured
(C.L. Backinger et al., 2008)	Use of other tobacco products among U.S. adult cigarette smokers: prevalence, trends and correlates	Re-analysis of cross-sectional studies. Data from the 1995/96, 1998, 2000, and 2001/02 TUS-CPS Survey were used to estimate concurrent use of tobacco among cigarette smokers among adults (18 years and older)  N = 552,804 (U.S.)	Cigarette smoking status  Frequency of smoking  Other tobacco use	ST use (chew or snuff) among cigarette smokers: 1995/1996: 0.86% 1998: 1.18% 2000: 0.93% 2001/2002: 0.97%  Concurrent tobacco use in the U.S. increased overall from 1995/96 to 1998 (0.88% to 1.76%), but decreased from 1998 to 2000 (1.48%), and 2001/02 (1.19%).	<i>Strengths:</i> Nationally representative  <i>Limitations:</i> Small sample of dual use, necessitating data collapse Possible confusion about product category terminology Limited inclusion of some product types in the TUS-CPS data.
(Bombard, Pederson, Nelson, & Malarcher, 2007)	Are smokers only using cigarettes? Exploring current polytobacco use among an adult population	Cross-sectional. Telephone survey (2003 Behavioral Risk Factor Surveillance System survey)  N = >50,000 (10 states)	Self-reported current tobacco use (daily or almost daily use)	Cigarettes: 22.4% ST use: 3.5% Polytobacco use: 3.4%  Polytobacco use more common among male smokers, with 26.0% using at least one other product, as compared with 4.4% of female smokers.	<i>Strengths:</i> Large sample size  <i>Limitations:</i> No differentiation between noncigarette products Self-report Lack of biochemical verification Limited geographical generalizability

(Raymond G. Boyle, St Claire, Kinney, D'Silva, & Carusi, 2012)	Concurrent use of cigarettes and smokeless tobacco in Minnesota	Cross-sectional telephone survey (Minnesota Adult Tobacco Survey, 1999-2010)  N = 5,968-12,580 adults (depending on year of survey) (Minnesota)	Current smoking (>100 lifetime cigarettes and daily/some days smoking)  ST use (past 30 day use)	Smokers using ST: 1999: 5.2% 2003: 5.0% 2007: 4.4% 2010: 9.6%  The prevalence of cigarette smokers who used ST increased between 2007 and 2010 (4.4% vs. 9.6%, $p < 0.05$ ), which was similar to the increase in ST use during this same time period (3.1% vs. 4.3%, $p < 0.05$ ).  Some-day smokers more likely to report ST use than daily smokers (17.3% vs. 7.3%, $p < 0.05$ ) and lighter smokers more likely than heavier smokers (13.7% vs. 5.5%, $p < 0.05$ ).	<i>Limitations:</i> Cross-sectional Self-report
(R. G. Boyle et al., 1998)	Use of smokeless tobacco by young adult females	Cross-sectional. Survey  N = 20 female ST users (upper Midwest)	ST use  Cigarette use	All the participants used moist snuff including Kodiak, Copenhagen®, and Skoal.  Concurrent smoking: Regular: 10% Occasional: 35% Tried: 30% Ex-smokers: 25%	<i>Limitations:</i> Small sample size Self-report Limited geographical generalizability
(Centers for Disease Control and Prevention, 1993)	Use of smokeless tobacco among adults - United States, 1991	The CDC's 1991 National Health Interview Survey-Health Promotion and Disease Prevention supplement (representative sample of the U.S. civilian, noninstitutionalized population aged greater than or equal to 18 years) collected information on snuff and chewing tobacco use and smoking. N=43,732 smokeless tobacco users in survey were used to provide national estimates.	Prevalence	The authors found that:  "In this report, one concern is that nearly one fourth of current smokeless tobacco users also smoke cigarettes."  "Among current users of smokeless tobacco, 22.9% (95% CI: 19.9-26.0) currently smoked, 33.3% (95% CI: 30.0-36.5) formerly smoked, and 43.8% (95% CI: 39.9-47.7) never smoked. In comparison, among current smokers, 2.6% (95% CI: 2.3-3.0) were current users of smokeless tobacco."	<i>Strengths:</i> Nationally representative sample  <i>Limitations:</i> May not reflect current tobacco product use behavior
(Cohen-Smith &	A comparison of male	Cross-sectional.	Tobacco use history	Dual use (current or former):	<i>Strengths:</i>

(Severson, 1999)	and female smokeless tobacco use	Telephone and in person interviews  N = 51 female ST users N = 59 male ST users (Pacific Northwest)	Patterns of use  Reasons for use	Males: 89.8% Females: 98%  Majority reported use of ST while quitting smoking (51.7% females and 58.8% males), and 33.3% of females and 28.8% of males reported use of ST as alternative to smoking.	Structured interview  <i>Limitations:</i> Small sample Self-report – recall bias Lack of matched samples between sexes Limited demographic and geographic generalizability
(Cooper et al., 2010)	Differences between intermittent and light daily smokers in a population of U.S. military recruits	Population-based group randomized prevention and cessation trial (1-year follow-up)  N = 5,603 U.S. Air Force nondaily or light daily smoking recruits (U.S.)	Tobacco use history  Risk factors	Relative to never use, the use of ST products either intermittently (OR = 1.98, $p < 0.001$ ), or daily (OR = 5.39, $p < 0.001$ ), increased the odds of being an intermittent smoker. ST may be associated with less smoking.	<i>Strengths:</i> Longitudinal  <i>Limitations:</i> Self-report – recall bias Limited generalizability Frequency/ intensity of use not captured.
(Cummings, Michalek, Carl, Wood, & Haley, 1989)	Use of smokeless tobacco in a group of professional baseball players	Cross-sectional. Questionnaire survey  N = 25 ballplayers (New York)	Current and past tobacco use	Current ST use: 17/25 Dual use: 6 used both chewing and dipping tobacco among 17 current ST users.	<i>Strengths:</i> Biochemical verification  <i>Limitations:</i> Small sample Limited generalizability to general population
(Jon O. Ebbert, Croghan, et al., 2010)	A pilot study to assess smokeless tobacco use reduction with varenicline	Pilot tobacco reduction trial of varenicline  N = 20 male ST users not interested in quitting (Minnesota)	Baseline tobacco use	1 out of 20 (5%) ST users reported current smoking (2 cigarettes/day).	<i>Limitations:</i> Small sample No biochemical verification

(Jon O. Ebbert, Severson, Croghan, Danaher, & Schroeder, 2009)	A randomized clinical trial of nicotine lozenge for smokeless tobacco use	Randomized, placebo-controlled multicenter clinical trial with 6-month follow-up to evaluate the efficacy of nicotine lozenge  N = 270 treatment-seeking ST users (Minnesota, Oregon)	Baseline tobacco use	29 out of 270 (8.1%) ST users reported current smoking.	<i>Strengths:</i> Randomized Controlled  <i>Limitations:</i> Limited generalizability Technical difficulties with biochemical verification No follow-up results on smoking abstinence in dual users.												
(Jon O. Ebbert, Croghan, Schroeder, & Hurt, 2013)	A randomized phase II clinical trial of high-dose nicotine patch therapy for smokeless tobacco users	Randomized cessation trial of high-dose nicotine replacement therapy patch  N = 52 treatment-seeking ST users (Minnesota)	Baseline tobacco use	Current use of other tobacco products amongst population of primary smokeless tobacco users: 0%	<i>Limitations:</i> Small sample Limited generalizability Issue with survey question comprehension												
(England et al., 2013)	Effects of maternal smokeless tobacco use on selected pregnancy outcomes in Alaska Native women: a case-control study	A population-based, case-control study using a retrospective medical record review (1997-2005)  N = 1,123 native women (western Alaska)	Self-reported tobacco use	<table><tr><td></td><td>Case</td><td>Control</td></tr><tr><td>Cigarettes only:</td><td>13.7%</td><td>10.7%</td></tr><tr><td>ST only:</td><td>51.2%</td><td>46.8%</td></tr><tr><td>Dual use:</td><td>8.2%</td><td>8.9%</td></tr></table>		Case	Control	Cigarettes only:	13.7%	10.7%	ST only:	51.2%	46.8%	Dual use:	8.2%	8.9%	<i>Limitations:</i> Small sample No differentiation of smokeless product type Limited generalizability
	Case	Control															
Cigarettes only:	13.7%	10.7%															
ST only:	51.2%	46.8%															
Dual use:	8.2%	8.9%															
(England et al., 2012)	Maternal smokeless tobacco use in Alaska Native women and singleton infant birth size	Retrospective review of medical records (1997-2005)  N = 497 Alaska native women (western Alaska)	Self-reported tobacco use	Percentage of women with maternal age $\geq 30$ y that continued to use: Cigarettes only: 11.9% ST only: 32.1% Dual use: 27.9%	<i>Limitations:</i> Small sample No differentiation of smokeless product type Limited generalizability												

(Fiedler et al., 1996)	Prevalence of tobacco use among first-term air force personnel before and after basic military training	Longitudinal study  N = 3,531 airmen (Texas)	Tobacco use at baseline and follow-up	<p>Females/Males Cigarettes only: 26.1%/27.6%  ST only: --/12.7%  Dual use: --/13%</p> <p>Baseline 20.7%/21%  Follow-up --/9.8%  --/16.4%</p> <p>Increase in dual use was not statistically significant.</p>	<p><i>Strengths:</i>  Longitudinal  Moderate sample size</p> <p><i>Limitations:</i>  Self-report  Limited generalizability</p>
(Fix et al., 2014)	Patterns and correlates of polytobacco use in the United States over a decade: NSDUH 2002-2011	Reanalysis of data from the NSDUH survey  N = 160,194 (U.S.)	<p>Past-year tobacco use</p> <p>Past-30 day tobacco use</p>	<p>2002 2011</p> <p>Prevalence:  Past-year polytobacco use: 8.7% 7.4%  (p &lt; 0.001)  Past-year single product use: 27.1% 24.1%  (p &lt; 0.001)</p> <p>Tobacco use rate:  Past-year ST use: 4.9% 5.4%  (p = 0.019)  Past-year cigarette use: 62.1% 59.9%  (p = 0.008)  Past-year cigarette/ST use: 3.2% 3.9%  (p &lt; 0.001)  Past 30-day cigarette/ST use: 3.0% 3.4%  (p &lt; 0.001)</p> <p>The proportion of polytobacco use, including cigarette/ST use, increased over time in those 26 years and older, even as overall tobacco use declined.</p>	<p>Large, nationally representative sample  Multiple-year data analysis</p> <p>Self-report  Cross-sectional  No assessment of nicotine dependence</p>
(Gillum, Obisesan, & Jarrett, 2009)	Smokeless tobacco use and religiousness.	<p>Cross-sectional.  Third National Health and Nutrition Examination Survey (1988-1994)</p> <p>N = 9,374 (U.S.)</p>	<p>Ever and current ST use</p> <p>Ever and current cigarette use</p>	<p>Among U.S. men (≥ 17 y), 5.74% (95% CI: 4.70-7.00%) were current users of ST  Among current ST users, 53% used chewing tobacco, 40% snuff, and 7% both; 28% were current cigarette smokers and 41% were former cigarette smokers.</p>	<p><i>Strengths</i>  Nationally representative  Large sample size  Biochemical verification of ST use</p> <p><i>Limitations:</i>  Missing data  Self-report – recall bias</p>



(Grasser & Childers, 1997)	Prevalence of smokeless tobacco use and clinical oral leukoplakia in a military population	Cross-sectional. Questionnaire survey  N = 214 soldiers (North Carolina)	Current ST use (past month)  Current cigarette use (not defined)	Cigarettes only: 29.0% ST only: 7.0% Dual use: 7.9% (8.7% of males; 3.2% of females)	<i>Limitations:</i> Cross-sectional Self-report Small sample Current use of cigarettes not defined. Limited generalizability
(Grier, Knapik, Canada, Canham-Chervak, & Jones, 2010)	Tobacco use prevalence and factors associated with tobacco use in new U.S. Army personnel	Analysis of cross-sectional survey (Soldier Health In-Processing) questionnaire (2000-2006)  N = 27,289 male and 3,856 female adult military students (Maryland)	Past 30-day cigarette smoking and ST use  Occasional use: < 20/30 days  Frequent use: ≥ 20/30 days	Both male and female ST users had higher odds of being a frequent smoker:  Occasional ST use (reference = no): Males: OR = 3.74; 95% CI: 3.28-4.27 Females: OR = 4.55; 95% CI: 2.33-8.88  Frequent ST use (reference = no): Males: OR = 2.56; 95% CI: 2.36-2.78 Females: OR = 3.31; 95% CI: 1.88-5.82  Both male and female smokers had higher odds of being a frequent ST user: Occasional smoking: Males: OR = 1.98; 95% CI: 1.68-2.33 Females: OR = 3.67; 95% CI: 1.40-9.64  Frequent smoking (OR [95% CI]): Males: OR = 2.58; 95% CI: 2.36-2.82 Females: OR = 4.81 95% CI: 2.58-8.93	<i>Strengths:</i> Assessed prevalence over time  <i>Limitations:</i> Limited generalizability
(C. K. Haddock, Klesges, Talcott, Lando, & Stein, 1998)	Smoking prevalence and risk factors for smoking in a population of United States Air Force basic trainees	Cross-sectional. Questionnaire survey (1995-1996)  N = 32,144 U.S. Air Force basic trainees (Texas)	Current smoking: regular smoking (at least once per day)	All Males Females ST use: 4.6% 6.0% 0.2%  ST use increased odds of being a smoker as compared with those for never smokers OR = 1.94; 95% CI: 1.61-2.34.	<i>Strengths:</i> Large sample size  <i>Limitations:</i> Limited generalizability

(C. Keith Haddock, Jitnarin, Poston Walker, Tuley, & Jahnke, 2011)	Tobacco use among firefighters in the central United States	Population-based cohort study  N = 677 male firefighters (Missouri)	Tobacco use history Smoking: past 30-days, ever, lifetime >100 cigarettes  ST: past 30-days  Breath CO	Firefighter: Career Volunteer Cigarette use: 13.6% 17.4% ST use: 18.4% 16.8%  Among smoking career firefighters, 30.5% also used ST.  Among smoking volunteer firefighters, 17.3% also used ST.	<i>Strengths:</i> Biochemical verification of smoking status  <i>Limitations:</i> Limited generalizability Cross-sectional
(D. Hatsukami et al., 1999)	Characteristics of smokeless tobacco users seeking treatment.	Randomized, placebo-controlled cessation trial  N = 402 treatment-seeking ST users (Minnesota)	Baseline tobacco use history	Ever smoking: 69.2% of ST users.  Of ever smokers: 24.5% were current smokers, with the majority smoking less than 1 cigarette per day (83.8%). 51.4% tried ST first. 45.1% reported history of being daily smoker. 25.9% reported ST use as aid to quit smoking. 14.0% reported smoking as an aid to quit ST 31.3% reported cigarettes as ST substitute.	<i>Limitations:</i> Excluded ST users who were regular smokers (>20 cigarettes per month)
(Hermes et al., 2012)	Smokeless tobacco use related to military deployment, cigarettes and mental health symptoms in a large, prospective cohort study among U.S. service members	Longitudinal. Survey with 2-year follow-up in a population-based sample (Millenium Cohort Study; 2001-2006)  N = 45,272 U.S. military service members (U.S.)	Past-year ST use Lifetime cigarette use (> 100 cigarettes)	ST use: Never smoker 32.6% 29.9% 37.2% Past smoker 19.3% 27.0% 27.1% Initiator/recidivist 22.1% 14.4% 16.0% Persistent smoker 26.1% 28.8% 19.7%	<i>Strengths:</i> Large sample Longitudinal  <i>Limitations:</i> Stratified sampling design may not reflect a random or complete sample of all eligible subjects Difficulties with initial or follow-up response rate.

(Nattinee Jitnarin, Haddock, Poston Walker, & Jahnke, 2013)	Smokeless tobacco and dual use among firefighters in the central United States	Longitudinal cohort study (2008-2010)  N = 353 male career firefighters (Missouri)	Baseline tobacco use	ST use only: 13.3% Dual users: 2.6%	<i>Limitations:</i> Cross-sectional Small sample size Limited geographical generalizability																
(N. Jitnarin, Poston, Haddock, Jahnke, & Day, 2015)	Tobacco use pattern among a national firefighter cohort	Longitudinal study (The impact of the Nutrition Environment in the Fire Service on Health and Safety”; 2010 and 2011)  N = 947 career firefighters (U.S.)	Baseline tobacco use	Cigarettes only: 34.5% ST use only: 53.2% Dual use: 12.2%	<i>Strengths:</i> Nationally representative of firefighters  <i>Limitations:</i> Cross-sectional Unable to determine whether smoking preceded or followed ST use Limited generalizability																
(Kim, England, Dietz, Morrow, & Perham-Hester, 2010)	Patterns of cigarette and smokeless tobacco use before, during, and after pregnancy among Alaska native and white women in Alaska, 2000-2003	Cross-sectional. Questionnaire survey (population-based Alaska Pregnancy Risk Assessment Monitoring System questionnaire (2000-2003)  N = 5,458 adult females (N = 1,528 Alaska natives) (Alaska)	Self-reported tobacco use before, during and after pregnancy	Pregnancy status (Alaska Natives only): <table><tr><td></td><td>Before</td><td>During</td><td>After</td></tr><tr><td>Cigarettes only:</td><td>38.5%</td><td>24.9%</td><td>32.8%</td></tr><tr><td>ST use only:</td><td>14.2%</td><td>14.6%</td><td>15.3%</td></tr><tr><td>Dual use:</td><td>6.4%</td><td>3.2%</td><td>4.6%</td></tr></table>		Before	During	After	Cigarettes only:	38.5%	24.9%	32.8%	ST use only:	14.2%	14.6%	15.3%	Dual use:	6.4%	3.2%	4.6%	<i>Limitations:</i> Cross-sectional Self-reported tobacco use Limited generalizability
	Before	During	After																		
Cigarettes only:	38.5%	24.9%	32.8%																		
ST use only:	14.2%	14.6%	15.3%																		
Dual use:	6.4%	3.2%	4.6%																		
(Klesges, Sherrill-Mittleman, Ebbert, Talcott, & Debon, 2010)	Tobacco use harm reduction, elimination, and escalation in a large military cohort	Rates of harm elimination, reduction, and escalation were evaluated in 5,225 U.S. Air Force airmen assigned to the health education control condition in a smoking cessation and prevention trial.	Harm elimination (e.g., tobacco cessation)  Harm reduction (e.g., from smoking to ST use)  Harm escalation (e.g., from smoking to dual use or from ST use to smoking or dual use)	The authors reported a dual use incidence of 4.8% at initiation of the study. After 12 months, approximately 25% of these individuals remained dual users.  They also described “Significant predictors of smokers becoming dual users as” age, gender, smoking history (greater number of pack-years associated with increased odds of harm escalation) and alcohol consumption.	<i>Limitations:</i> Military population with only 1 year of follow-up and forced tobacco abstinence																

(Klesges et al., 2011)	Impact of differing definitions of dual tobacco use: implications for studying dual use and a call for operational definitions	Cross-sectional study on dual use definitions  N = 36,013 Air Force recruits (Tennessee, Missouri, Minnesota)	Tobacco use variables:  Type of tobacco (cigarettes, ST, cigars, pipes, clove cigarettes, bidis)  Frequency of use (daily/nondaily)	Estimates of prevalence of dual use vary by up to 50-fold, depending upon the definition of dual use (0.5%-25.3%). When using a more stringent definition of tobacco use of concomitant ST and cigarette use, the prevalence ranges decreased, but still are approximately fourfold (2.0%-9.7%).  Daily use of cigarette or ST and at least nondaily use of the other substance yields a prevalence estimate of 3.3%.	<i>Strengths:</i> Large sample size Systematic categorization of dual use  <i>Limitations:</i> Disproportionate number of males, minorities, and individuals from lower incomes
(Klosky et al., 2013)	Smokeless and dual tobacco use among males surviving childhood cancer: a report from the Childhood Cancer Survivor Study	Cross-sectional. Survey (Childhood Cancer Survivor Study 2007 survey)  N = 3,378 male cancer survivors (U.S.)	Prevalence of ST use and dual tobacco use.	Current use: ST only: 8.3% Dual use: 2.3%  Lower likelihood of ST and dual use in survivors as compared with that for population males (NSDUH) (prevalence rate = 0.37; 95% CI: 0.29-0.46).	<i>Limitations:</i> Cross-sectional Self-report, possible underreporting of use.
(Lando, Haddock, Klesges, Talcott, & Jensen, 1999)	Smokeless tobacco use in a population of young adults	Cross-sectional. Questionnaire survey (1995-1996)  N = 32,144 military trainees (U.S.)	History of tobacco use (smoking and smokeless)	Current smokers using ST: 4.6% Never smokers using ST: 4.1%	<i>Strengths:</i> Large sample size  <i>Limitations:</i> Limited questions about tobacco use Lack of product specificity

(Lee Joseph, Goldstein, Ranney, Crist, & McCullough, 2011)	High tobacco use among lesbian, gay, and bisexual populations in West Virginian bars and community festivals	Cross-sectional. Questionnaire  N = 386 lesbian, gay, and bisexual individuals (West Virginia)	Current use (every day, some days, not at all)	Cigarettes ST Cigarette smokers --- 6% ST users 60% ---	<i>Limitations:</i> Cross-sectional Small sample size Results may not generalize to other lesbian, gay, and bisexual communities
(Lee, Hebert, Nonnemaker, & Kim, 2014)	Multiple tobacco product use among adults in the United States: cigarettes, cigars, electronic cigarettes, hookah, smokeless tobacco, and snus	Cross-sectional. Telephone survey (2012 RTI National Adult Tobacco Survey)  N = 3,627 adults (U.S.)	Current use patterns of tobacco products	Cigarettes only: 14.9%  Noncigarette product only: 6.6%  Cigarette and noncigarette product: 6.9% ST and cigarettes: 0.4%	<i>Limitations:</i> Cross-sectional Small sample size
(Mazurek, Syamlal, King, & Castellan Robert, 2014)	Smokeless tobacco use among working adults - United States, 2005 and 2010	CDC analyzed National Health Interview Survey data to estimate the proportion of U.S. working adults who used ST in 2005 and 2010, by industry and occupation.  N = 15,649 and 19,445 U.S. working adults in 2010 and 2005, respectively	Prevalence	The authors reported:  "Among working adults who currently smoke cigarettes, the proportion who currently used smokeless tobacco (i.e., dual users) was 4.1% in 2005 and 4.2% in 2010."  "In 2010, dual use was greatest among the following subgroups of working adult smokers: those aged 18–24 years (6.3%), males (7.3%), non-Hispanic whites (3.9%), those with no more than a high school education (4.5%), those with annual household income ≥ \$75,000 (4.8%), and those living in the Midwest (5.3%). Among adult workers, the average number of cigarettes smoked per day was significantly higher among dual users (15.5) compared with those who used cigarettes only (12.1) (p < 0.05).	<i>Limitations:</i> Use of self-reported data that were not validated by biochemical tests Limited sample size Low response rate Lack of inclusion of all ST products.

(Morgan, 2001)	Evaluation of an educational intervention for military tobacco users	One-time tobacco intervention study with 1-month follow-up  N = 151 male soldiers (Kentucky)	Baseline tobacco use (not specified)	Cigarettes only: 51% ST only: 22% Dual use: 27%	<i>Limitations:</i> Small sample Lack of control
(E. A. Mumford, Levy, Gitchell, & Blackman, 2006)	Smokeless tobacco use 1992-2002: trends and measurement in the Current Population Survey-Tobacco Use Supplements	Reanalysis of data from the TUS-CPS (1992–2002)  N = 125,000-239,000 adults/year	Ever use  Current use (every day, some days)  Past 30-day use (number of days)	Current use: 1992/93 2001/02 Cigarette use: 24.5% 21.0% ST use: 2.3% 1.5% Dual use: 0.49% 0.28%  Overall decline in cigarette, ST and dual use.	<i>Strengths:</i> Large sample Nationally representative  <i>Limitations:</i> Cross-sectional Did not differentiate between snuff and chewing tobacco
(Elizabeth A. Mumford et al., 2005)	Tobacco control policies and the concurrent use of smokeless tobacco and cigarettes among men, 1992-2002	Reanalysis of data from the TUS-CPS (1992–2002)  N = 41,000–64,000 male adults/year (U.S.)	Ever use  Current use (every day, some days)	Smokers who currently use ST: < 5% ST users who currently smoke: ~ 25%  Overall decline in cigarette, ST and dual use over time.	<i>Strengths:</i> Large sample Nationally representative  <i>Limitations:</i> Cross-sectional Did not differentiate between snuff and chewing tobacco
(Mushtaq, Williams, & Beebe, 2012)	Concurrent use of cigarettes and smokeless tobacco among U.S. males and females	Reanalysis of data from the 2010 Behavioral Risk Factor Surveillance System  Adults (U.S.), sample size not specified	Current use (some days or every day)  Concurrent use: daily/someday user of ST and cigarettes	Males Females Dual use: 1.6% 0.3% Cigarettes only: 17.4% 14.8% ST use only: 4.2% 0.5%  Prevalence of dual use higher among American Indian/Alaska natives, younger, single, unemployed, less educated, heavy drinkers.	<i>Limitations:</i> Self-report Noncoverage bias due to sampling method Low response rates

(Noonan & Duffy, 2012)	Smokeless tobacco use among operating engineers	Cross-sectional. Survey  N = 498 operating engineers (Michigan)	Past 30-day use	Cigarettes only: 29% ST only: 13% 15% of ST users also used cigarettes Past month smoking associated with 60% lower likelihood to use ST (OR = 0.402; 95% CI: 0.191–0.843; p = 0.017).	<i>Limitations:</i> Cross-sectional Self-report Small sample Limited generalizability
(Noonan & Duffy, 2014)	Factors associated with smokeless tobacco use and dual use among blue collar workers	Reanalysis of data from the NSDUH (2009)  N = 5,392 blue collar workers (U.S.)	Past-month cigarette or ST use	ST users: 5.3% Dual users: 4.2%  Cigar smokers had higher odds of being dual user of ST and cigarettes than those dual users who did not smoke cigars (ORs = 2.40 vs. 0.88).	<i>Strengths:</i> Nationally representative  <i>Limitations:</i> Cross-sectional Self-report
(Nugent et al., 2014)	Familial aggregation of tobacco use behaviors among Amish men	Cross-sectional study  N = 1,216 Amish males (Pennsylvania)	Ever use  Current use	Ever use of more than one tobacco product: 7.7%  In ever users, current use of more than one (not defined) tobacco product: 16.2%	<i>Limitations:</i> Cross-sectional Small sample Self-report Unvalidated method of quantifying the amount and specific type of tobacco used.
(O'Connor et al., 2007)	Smokers' beliefs about the relative safety of other tobacco products: findings from the ITC Collaboration	Reanalysis of data from the International Tobacco Control Four-Country Survey (telephone; 2002-2004)  N = 13,322 adult smokers (Australia, Canada, United Kingdom, U.S.)	Past-month use of “other” tobacco products (cigars, cigarillos, bidis, pipes, chewing tobacco, snuff or other)  Note: analysis collapsed chewing tobacco and snuff into single ST category	In the U.S, dual use of cigarettes and ST was 2.3% in Wave 1, decreasing to 0.7% in Wave 3.  Dual use was highest in the U.S. as compared with dual use in other countries included in the survey.	<i>Strengths:</i> International sampling  <i>Limitations:</i> Cross-sectional Did not assess frequency/amount of use other than last-month use.
(Peterson et al., 2007)	Smokeless tobacco use in military personnel	Randomized ST cessation trial  N = 785 active duty military personnel (U.S.)	Baseline tobacco use	20% were dual users, although 64% of these individuals indicated that they smoked ≤ 10 cigarettes per day.	<i>Limitations:</i> Cross-sectional Self-report Small sample

(Richardson, Pearson, Xiao, Stalgaitis, & Vallone, 2014)	Prevalence, harm perceptions, and reasons for using noncombustible tobacco products among current and former smokers	Reanalysis of data from 3rd follow-up of Legacy’s EX smoking cessation campaign study (2011)  N = 1,487 current and former smokers (U.S.)	Current smoker: some days/every day	Cigarette smokers: 51.4%  Cigarette smoker and ever use of any noncombustible product: 33.6% (19.0% for ST)  Dual users smoke on average more cigarettes/d than exclusive smokers (17.1 vs. 15.0 cigarettes/day).	<i>Limitations:</i> Cross-sectional Did not measure frequency/intensity of use of noncombustible tobacco products.
(Spangler et al., 2001)	Dual Tobacco use among Native American adults in southeastern North Carolina	Cross-sectional. Telephone survey  N = 400 adult Lumbee Indians (North Carolina)	Current cigarette smoking: (≥ 100 cigarettes in lifetime and current “yes” response)  Current ST use: past 30-days	Current smoking: 26% Current ST use: 18.5% Dual use: 4.8% (18.3% of current smokers and 25.7% of current ST users reported dual tobacco use)  Dual users reported fewer cigarettes per day than exclusive smokers.	<i>Limitations:</i> Cross-sectional Sampling bias Self-report Limited generalizability Small sample size
(Spangler et al., 1999)	Epidemiology of tobacco use among Lumbee Indians in North Carolina	Cross-sectional. Telephone survey  N = 400 adult Lumbee Indians (North Carolina)	Current cigarette smoking  Current ST use	Current smoking: 21.8% Current ST use: 13.5% Dual use: 4.3%	<i>Limitations:</i> Cross-sectional Sampling bias Self-report Limited generalizability Small sample size
(Spangler et al., 1997)	Prevalence and predictors of tobacco use among Lumbee Indian women in Robeson County, North Carolina	Longitudinal. In-person interviews  N = 982 adult female Lumbee Indians (North Carolina)	ST: ever use, current and former  Cigarettes: current, former	Current use: Cigarette smoking: 23.7% ST use: 20.6% Dual use: 3.2%	<i>Limitations:</i> Cross-sectional Sampling bias Self-report Limited generalizability
(Talcott et al., 2013)	Tobacco use during military deployment	Longitudinal. Survey  N = 278 U.S. Air Force Security Forces Personnel (Texas)	Cigarette and ST use  Frequency of use	Dual use: Predeployment: 9.4% During deployment: 12.9% Postdeployment: 7%  Nonsignificant changes in dual use patterns over time.	<i>Strengths:</i> Longitudinal Powered to evaluate trajectories  <i>Limitations:</i> Self-report - recall bias at baseline Nonrandom sample



(Timberlake, 2008)	A latent class analysis of nicotine-dependence criteria and use of alternate tobacco	Latent class model analysis of data from Wave III of the National Longitudinal Study of Adolescent Health  N = 4,517 regular cigarette smokers (U.S.)	Alternate tobacco use (ST, cigars, bidis; past-month)	43.1% of male and 23.0% of female smokers reported past month use of ST, cigars or bidis.  Alternate tobacco use is correlated with nicotine dependence among smokers. Light-to-medium smokers were the most frequent users of alternate tobacco.	<i>Strengths:</i> Nationally representative  <i>Limitations:</i> Cross-sectional Limited measures for alternate tobacco use and nicotine dependence
(Tomar, 2002)	Snuff use and smoking in U.S. men: implications for harm reduction	Reanalysis of data from the 1998 National Health Interview Survey  N = 13,865 adult males (U.S.)	Tobacco use history  Quit attempts	Population distribution: Current smoking: 26.4% Current ST use: 3.6% Current dual use: 1.1%  Current smoking most prevalent in “some days” ST users (38.9%) and lowest in daily ST users (19.2%).	<i>Strengths:</i> Large sample Nationally representative of males  <i>Limitations:</i> Sequence of product use not known Age at initiation of ST unknown Self-report - recall bias Frequency/intensity of ST use not captured Reasons for switching not captured
(Vander Weg et al., 2005)	Prevalence and correlates of lifetime smokeless tobacco use in female military recruits	Cross-sectional. Questionnaire survey  N = 9,087 female Air Force recruits (Texas)	Tobacco use history	Current daily or occasional ST use: 0.4%  Lifetime ST use (reference = never-smoker): Current smokers: OR = 3.80; 95% CI: 2.42-5.94	<i>Strengths:</i> Large sample size of underrepresented group (females)  <i>Limitations:</i> Self-report

(Vander Weg et al., 2008)	Prevalence of alternative forms of tobacco use in a population of young adult military recruits	Cross-sectional. Questionnaire survey (1999-2000)  N = 31,107 adult military recruits (U.S.)	Alternative tobacco use	Current (daily or occasional) ST use: 6.7%  Cigarette smokers were more likely to use ST (OR = 3.31; 99% CI: 2.93-3.73; p < .001)	<i>Limitations:</i> Cross-sectional Limited generalizability Self-report
(Vijayaraghavan, Pierce, White, & Messer, 2014)	Differential use of other tobacco products among current and former cigarette smokers by income level	Reanalysis of data from National Surveys on Drug Use and Health results (2006-2011)  N = 54,239 former and current smokers (U.S.)	Use of other tobacco products (daily, monthly, past year)	Daily ST use: 2.3-3.6% in current smokers 2.8-6.6% in former smokers.  Current smokers more likely to use ST in past year than former smokers (AOR = 1.14, 95% CI: 1.01–1.28)	<i>Strengths:</i> Large sample Nationally representative  <i>Limitations:</i> Self-report Cross-sectional Did not differentiate between episodic and regular use of other tobacco.
(S.-H. Zhu et al., 2009)	Quitting cigarettes completely or switching to smokeless tobacco: do U.S. data replicate the Swedish results?	Longitudinal study. Data from two TUS-CPS 2002 (2001-2003) (1-year follow-up)  N = 15,056 adults (U.S.)	Tobacco user status	Male tobacco user status change (%):  Smokers to dual users: 2.2 (95% CI: 1.4-3.5)  ST users to dual users: 1.8 (95% CI: 0.6-5.5)  No change in dual use: 45.0 (95% CI: 29.7-61.3) Dual users to smokers: 37.0 (95% CI: 23.2-53.4)	<i>Strengths:</i> Longitudinal Nationally representative sample
(Shu-Hong Zhu et al., 2013)	The use and perception of electronic cigarettes and snus among the U.S. population	Cross-sectional. Telephone survey (2012)  N = 10,041 adults (U.S.)	Smoking history  Use of snus, e-cigarettes (current use: every day or some days)	Dual use (%): Males: 3.20 (95% CI: 2.10-4.30) Females: 1.70 (95% CI: 0.51-2.82)	<i>Strengths:</i> Large sample Nationally representative  <i>Limitations:</i> Cross-sectional Self-report ST not included

U.S. = United States.

#### **7.5.2-1.3.4. Demographic and Behavioral Aspects of Those Consumers Who Use Both Moist Smokeless Tobacco and Cigarettes**

The following sections will address the demographic (Section 7.5.2-1.3.4.1) and behavioral aspects of dual users, including use behaviors (Section 7.5.2-1.3.4.2), nicotine dependence (Section 7.5.2-1.3.4.3), and cessation (Section 7.5.2-1.3.4.4). The literature search yielded 24 publications that assessed the demographic and behavioral correlates associated with dual use. As noted in Section 7.5.2-1.3.1, for the purposes of this review, dual users were limited to individuals who use both cigarettes and ST only (information on dual use of other combustible tobacco products, e.g., cigars, are not included) because this type of dual use may confer the greatest health risks and smoking represents the predominant form of tobacco use in the U.S.

The studies included adolescent, young adults (i.e., college students), and adult samples. Some of the studies identified were specifically designed to investigate dual use; whereas, in other cases, dual use information was extracted from other data presented within the study. All the studies summarized were conducted in the U.S., and in most cases, data were limited to the dual use of ST and cigarettes. A summary of the limitations of this data set is included in Section 7.5.2-1.3.2.

In general, the literature review indicates that dual use of ST and cigarettes is less commonly reported than exclusive cigarette smoking. Consistent with the demographic characteristics of exclusive ST users, individuals who report dual use are typically younger, unmarried, white males with lower educational background and socioeconomic status. Dual users have been found to smoke fewer cigarettes than exclusive smokers; however, there is also evidence suggesting that dual users may demonstrate more signs of nicotine dependence than those who consume only a single product. In some individuals the dual use of ST and cigarettes is a method of smoking cessation, but most data suggest that although dual users are more likely to reduce the amount they smoked, they are less likely to stop all tobacco use altogether.

##### **7.5.2-1.3.4.1. Demographics**

As noted in Section 7.5.2-1.1, the initiation of tobacco use rarely begins with both cigarette smoking and ST use. In fact, most dual users begin using tobacco with the exclusive use of cigarettes. Most tobacco users do not begin using both cigarettes and ST and only a small percentage of exclusive users became dual users (Tomar, 2003; S.-H. Zhu et al., 2009). For example, Tomar et al. (Tomar, 2003) found that only 3.6% of exclusive smokers and 14.3% of exclusive ST users at baseline became dual users after four years. Additionally, Zhu et al. (2009) reported that among males who exclusively smoked cigarettes in 2002, 2.2% became dual users by 2003; while among males who exclusively used ST in 2002, 1.8% became dual users.

In terms of demographic characteristics of dual users, research in adolescents and adults suggest many similarities in the demographic characteristics of dual users and ST users (Section 7.5.3-1 and Section 7.5.3-2) (Olmsted, Bray, Reyes Guzman, Williams, & Kruger, 2011; Renner et al., 2013; Brad Rodu & Cole, 2009; Wetter et al., 2002). Specifically, dual users of ST and cigarettes are more likely to be white males from the southern regions

of the U.S. who are generally younger, with lower educational background, lower socioeconomic status, and unmarried (McClave-Regan & Berkowitz, 2011; S.-H. Zhu et al., 2009). Studies with selected special populations, such as military recruits and Alaskan native people, suggest a similar demographic regarding age and educational background, but also report that some females have adopted the practice of dual use, although the numbers are not large (Olmsted et al., 2011; Renner et al., 2013).

#### **7.5.2-1.3.4.2. Use Behaviors**

Published studies suggest that, although dual users may smoke cigarettes, which are recognized as the most risky form of tobacco use, they generally smoke fewer cigarettes than exclusive smokers. Rodu and Cole (2009) examined data from the 2000 (N = 4.14 million ST users) and 2005 (N = 4.44 million ST users) U.S. National Health Interview Surveys and noted that in 2000, daily smokers who also used ST every day consumed significantly fewer cigarettes on average than exclusive smokers (mean: 13 vs. 20 cigarettes per day,  $p \leq 0.05$ ) (Brad Rodu & Cole, 2009). This difference was also noted in the 2005 survey (13 vs. 19 cigarettes per day,  $p \leq 0.05$ ) (Brad Rodu & Cole, 2009). In a study of 4,886 adult male tobacco users by Wetter et al. (2002), although the overall reported use of cigarettes by both exclusive smokers and dual users was higher than that found by Rodu and Cole, the directional reduction was still apparent (approximately 20 cigarettes per day for concomitant [dual] users and approximately 25 cigarettes per day for exclusive smokers,  $p \leq 0.001$ ).

Cooper and colleagues (Cooper et al., 2010) used data from a survey of U.S. military recruits to analyze concomitant ST and cigarette use behaviors among light smokers (N= 2,469 subjects; daily, < 10 cigarettes per day) and intermittent smokers (N= 3,134 subjects; nondaily). The authors found that use of ST products either intermittently, (OR = 1.98; 95 percent CI: 1.41-2.79), or daily, (OR = 5.39; 95 percent CI: 3.36-8.63), increased the odds of being an intermittent smoker, and suggested that greater ST use is associated with less smoking. Although the reasons for this are unclear, it is possible that for some tobacco users, intermittent use of one tobacco product serves as a substitute for another product. This is consistent with some reports of cigarette smokers using ST as a substitute when smoking is not permitted (McClave-Regan & Berkowitz, 2011; S.-H. Zhu et al., 2009).

#### **7.5.2-1.3.4.3. Nicotine Dependence**

Some studies of nicotine dependence characteristics and behaviors suggest that those who use multiple tobacco products may elicit more signs of nicotine dependence than those who consume only a single product (Apelberg et al., 2014; Kram et al., 2014). Using data from the National Youth Tobacco Survey (NYTS), Apelberg et al. (2014) examined dependence symptoms such as craving, irritability, or time to first cigarette and found that of the 3,454 adolescent current tobacco users, adolescents who reported the use of multiple tobacco products were more likely to report strong cravings (OR = 1.6, 95% CI: 1.3-1.9), strong desire to use (OR = 1.9, 95% CI: 1.4-2.4), and greater irritability and restlessness (OR = 1.3, 95% CI: 1.1-1.6) as compared with what was reported by single product users. In addition, multiple product users were greater than 2 times more likely to want to use tobacco within 30 minutes of waking (OR = 2.3, 95% CI: 1.6-3.1), suggesting a higher level of nicotine dependence. It is important to note, however, that the data in this study may be confounded

by the inclusion of multiple tobacco products (e.g., cigars, hookahs, pipes, e-cigarettes) in the characterization of “polytobacco user.”

A recent study conducted in a sample of 8,956 U.S. Air Force personnel used questions from the Fargeström Test of Nicotine Dependence (FTND) for ST and cigarettes to measure nicotine dependence in individuals who were smokers, ST users, and dual users with various usage frequencies (Kram et al., 2014). This study found that those individuals who were daily users of both cigarettes and ST had higher levels of nicotine dependence than dual users who used only one of the tobacco types daily (i.e., daily ST users/nondaily smokers and daily smokers/nondaily ST users). Overall, daily users of both cigarettes and ST were approximately 3 times more likely to have higher levels of nicotine dependence (OR = 2.72 to 2.84 depending on dual user group). Timberlake et al. (2008) performed a latent class analysis using 2001-2002 data (Wave III; 4,517 current cigarette smokers) from the National Longitudinal Study of Adolescent Health. This analysis utilized six elements of the FTND and four measures of past-month tobacco use. Although this analysis may have been confounded by the inclusion of multiple tobacco products (i.e., ST, cigars, and bidis) in the definition of alternate tobacco, the authors concluded that light smokers who used alternate tobacco products had a greater likelihood of being nicotine dependent than those who did not.

In contrast to studies suggesting greater nicotine dependence among dual users, Renner et al. (2013) were unable to find a significant relationship between heavier individual tobacco use and higher levels of addiction in a sample of 400 southwestern Alaska native people, a population that reports high levels of tobacco use, dual product use, and early tobacco use. In this study, the mean (SD) FTND scores were 2.6 (2.1) among cigarette users and 1.9 (1.9) among dual users. Despite attempts to examine dependence issues among dual users, no conclusive evidence is available to determine which product used by dual users might drive nicotine dependence. As discussed by Timberlake, genetics, smoking practices (e.g., amount of inhalation), and cofactors such as depression account for most variation seen in nicotine dependence among smokers (Timberlake, 2008).

#### **7.5.2-1.3.4.4. Cessation**

Dual users are more likely to reduce smoking intensity or to cease smoking cigarettes than exclusive smokers (Frost-Pineda et al., 2010). This is despite the fact that, at least for the U.S. cohorts assessed herein, dual users as a group have a higher prevalence of demographic variables that are typically associated with lower rates of smoking cessation, such as younger age, lower educational attainment (a strong correlate with poverty), and unmarried status (e.g., (Wetter et al., 2002; S.-H. Zhu et al., 2009)). Rodu and Cole (2009) noted that among a national sample of ST users who were former smokers, stopping smoking all at once was the most prevalent smoking cessation approach (900,000; 95 percent CI: 762,000–1,038,000) followed by switching to ST (120,000; 95 percent CI: 54,000-186,000), and smoking reduction (46,000; 95 percent CI: 8,000-84,000). In contrast to the potential for the use of ST to reduce cigarette consumption, Tomar (2003) reported that, based on a national sample of 3,996 adolescent males, ST use may increase the likelihood of subsequent cigarette smoking, suggesting that ST use was a method for supplementing nicotine for some smokers.

Furthermore, some data suggest that dual users may be less likely to become completely tobacco abstinent because of continued ST use (Frost-Pineda et al., 2010).

Zhu et al. (S.-H. Zhu et al., 2009) calculated population-weighted rates of switching and quitting smoking after 1-year follow-up. After the 1-year follow-up in 48 male dual users, 45% continued to use both, 37% stopped using ST and only smoked cigarettes, 4.9% quit smoking but continued ST, and 13% stopped both smoking and ST use (18% smoking cessation rate overall). In contrast, the percentage of male tobacco users who quit smoking 1 year later and the percentage who did not smoke or use ST 1 year later were lowest for the 1,105 baseline exclusive cigarette smokers (11.6% quit smoking, 11.3% quit cigarettes and did not use ST). Usage appears most stable for exclusive cigarette smoking, followed by exclusive ST and least stable for dual users.

Another U.S. study evaluated data collected from participants in the National Cancer Institute Working Well Trial Wetter et al. (2002). In this study 4,886 men who were assessed by survey at baseline were followed up after 4 years. Data from the 4-year follow-up survey revealed that, of the dual users, 28.7% had stopped smoking as compared with 17.1% of exclusive smokers. In contrast, 11.3% of dual users were completely tobacco abstinent as compared with 15.7% of exclusive smokers. Almost 80% of exclusive smokers continued to exclusively smoke, while 27% of dual users became exclusive smokers.

Although dual users may be more likely to stop smoking than exclusive smokers, nicotine dependence remains a serious concern among any tobacco user population, and as noted in Section 7.5.2-1.3.4.4 some studies suggest greater levels of nicotine dependence among dual users. Nonetheless, the collective trajectory data from independent studies in the U.S., which included follow-up periods from 1 to 10 years, suggest that, over time, dual users are less likely to stop all tobacco use, but they are more likely to reduce smoking intensity (i.e., transition away from cigarettes).

#### **7.5.2-1.3.5. Summary**

Overall, the prevalence of dual use of ST and cigarettes is lower than that of exclusive cigarette smoking; however, among those who report sustained ST use, the prevalence of concurrent cigarette smoking is higher than what is observed among those who report sustained cigarette smoking and who also use ST. Consistent with the demographic characteristics observed in exclusive ST users, dual users are more likely to be younger, unmarried, white males with lower educational background and socioeconomic status. With respect to use behaviors, data suggest that dual users smoke fewer cigarettes than exclusive smokers, which supports the notion that in some dual users, one tobacco product serves as a substitute for another product. There is also some evidence that suggests dual users may exhibit more signs of nicotine dependence than those who consume only a single product. However, it is not possible to conclusively determine which products used might be contributing to an individual’s nicotine dependence. With respect to dual use as a method of smoking cessation, the data suggest that, compared with exclusive smokers, dual users are less likely to stop all tobacco use over time, but they are more likely to reduce smoking intensity.

Table 7.5.2-1-3 presents a brief synopsis of the 24 publications identified as having data pertaining to demographics and use behaviors associated with dual use.



**Table 7.5.2-1-3: Literature Evaluating Demographics and Behavioral Aspects of Dual Use of Moist Smokeless Tobacco and Cigarette Smoking**

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
<i>Adolescents</i>					
(Apelberg et al., 2014)	Symptoms of tobacco dependence among middle and high school tobacco users: results from the 2012 National Youth Tobacco Survey	Cross-sectional. Survey (2012 NYTS)  N = 3,454 adolescent current users (U.S.)	Demographics  Tobacco Use (past 30-day use)  Tobacco dependence symptoms	<p>Polytobacco user characteristics: male, use tobacco more frequently, tried before age 11</p> <p>Single-product user characteristics: black, non-Hispanic</p> <p>Users with <math>\geq 1</math> dependence symptom (%):  Polytobacco users: 62.9 (95% CI: 59.0-66.6)  Single-product users: 36.0 (95% CI: 32.2-40.0)</p> <p>Polytobacco users compared with single-product users (AOR):  Strong cravings: 1.6 (95% CI: 1.3-1.9)  Strong desire to use: 1.9 (95% CI: 1.4-2.4)  Irritable or restless when not using tobacco for a while: 1.3 (95% CI: 1.1-1.6)  Use tobacco within 30 minutes of waking: 2.3 (95% CI: 1.6-3.1)</p> <p>Increased reporting of dependence symptoms in adolescent tobacco users associated with polytobacco use, increased frequency of use, earlier age at first use, and female sex.</p>	<p><i>Strengths:</i>  Large Sample size  Geographic representation</p> <p><i>Limitations:</i>  Polytobacco use included a wide array of products other than ST.</p>



Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Coogan, Geller, & Adams, 2000)	Prevalence and correlates of smokeless tobacco use in a sample of Connecticut students.	Cross-sectional. Survey  N = 12,565 Grades 4-8 N = 19,293 Grades 9-12 (Connecticut)	ST use  Risk-taking  Psychological distress	ST users vs. nonusers: Smoked cigarettes (54.3% vs. 17%; $p < 0.001$ ) Smoked heavily (15.4% vs. 2.5%; $p < 0.001$ )  Compared with male ST users ( $n = 335$ ) or smokers ( $n = 1591$ ), a significantly higher proportion of male dual users ( $n = 398$ ) reported ( $p < 0.001$ ): <ul style="list-style-type: none"> <li>• Current use of marijuana</li> <li>• Cocaine and other drugs</li> <li>• Drinking alcohol</li> <li>• Getting drunk</li> <li>• Receiving poor grades in school</li> <li>• No plans for postsecondary</li> <li>• Risky behavior (e.g., no seat belt, fighting, driving drunk)</li> <li>• Other measures of psychological distress</li> </ul> Prevalence of most health compromising and risk-taking behaviors, and indicators of stress, are highest among dual users of cigarettes and ST, lowest among exclusive users of ST, and intermediate among exclusive users of cigarettes	<i>Strengths:</i> Large sample size  <i>Limitations:</i> Cross-sectional Limited geographic and demographic representation Self-report Nonrandom sample

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Kerby, Brand, & John, 2003)	Anger types and the use of cigarettes and smokeless tobacco among Native American adolescents	Cross-sectional. Survey  N = 513 Native American students Grades 6, 8, and 10 (U.S.)	Tobacco use  Anger responses	37 (7.2%) report dual use  Externalizing factor (drugs, alcohol, physical fighting, break something, verbal argument, drive vehicle) related to dual use (Pearson’s $r = 0.36$ , $p < 0.001$ ), as well as cigarette ( $r = 0.54$ , $p < 0.001$ ) and ST use ( $r = 0.37$ , $p < 0.001$ ). 24% of externalizing type used both cigarettes and ST in the past 30 days. Externalizing type was about 10 times more likely to smoke, about 6 times more likely to use ST, and about 8 times more likely to show dual use. The majority of dual users (61%) were the externalizing type.  Internalizing factor (cry, music, thinking of hurting self, go somewhere alone, pray) was related to cigarette use ( $r = 0.12$ , $p = 0.006$ ), but not ST use or dual use.  Adaptive (ride bike, exercise, go for walk)f anger response did not correlate with tobacco use.	<i>Strengths:</i> National sample Unique sample of Native Americans  <i>Limitations:</i> Cross-sectional No information on tribal membership Modest internal reliability of anger scales
(Murray, Roche, Goldman, & Whitbeck, 1988)	Smokeless tobacco use among ninth graders in a north-central metropolitan population: cross-sectional and prospective associations with age, gender, race, family structure, and other drug use	Cross-sectional. Survey  N = 4,249 9th grade students (Minnesota)	Demographics  Tobacco and other drug use	Lifetime ST use: Smoking (any) 60.8% vs. 34.5% nonsmoking  Past-week ST use: Smoking (any) 20.0% vs. 6.0% nonsmoking  Lifetime ST use in smokers vs. nonsmokers (OR = 4.24, 95% CI, 2.80-6.42)  ST use was generally more common among those who smoked, drank, or used marijuana, based either on the cross-sectional or on the prospective data.	<i>Strengths:</i> Large sample size Complexity of analyses  <i>Limitations:</i> Tobacco use practices may or may not represent the general population.

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Nasim, Blank, Cobb, & Eissenberg, 2012)	Patterns of alternative tobacco use among adolescent cigarette smokers	Cross-sectional. Survey (2009 NYTS)  N = 2,746 current (past 30-day) smokers (U.S.)	Tobacco use  Demographics  Attitudes  Risk perception  Parental/peer use  Tobacco dependence	<p>51.9% of smokers reported alternative tobacco use.</p> <p>Alternative tobacco use reported by:  21.8% of intermittent smokers  25.1% of daily smokers  83.8% of daily smokers-Indulgent</p> <p>20.8% of current smokers reported ST use, of those:  8.6% were nondaily light smokers  17.3% were chippers  35.1% were chippers-Indulgent</p> <p>Smokers reporting current ST use:  males &gt; females (<math>\chi^2 = 199.13</math>, <math>p &lt; 0.01</math>)  whites &gt; blacks (<math>\chi^2 = 15.55</math>, <math>p &lt; 0.01</math>)  or Hispanics (<math>\chi^2 = 23.43</math>, <math>p &lt; 0.01</math>)</p> <p>Chippers-Indulgent were:</p> <ul style="list-style-type: none"> <li>• 1.14–1.52 times more likely than nondaily light smokers to have peers who smoked cigarettes (<math>p &lt; 0.01</math>)</li> <li>• 1.09–1.38 times more likely to perceive smoking as cool (<math>p &lt; 0.01</math>)</li> <li>• 1.16–1.51 times more likely to perceive smoking 1 or 2 years before quitting as not risky (<math>p &lt; 0.01</math>).</li> </ul>	<p><i>Strengths:</i>  Complex modeling</p> <p><i>Limitations:</i>  Cross-sectional  Self-report – recall bias  Survey did not include newer tobacco products</p>

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Simon, Sussman, Dent, Burton, & Flay, 1993)	Correlates of exclusive or combined use of cigarettes and smokeless tobacco among male adolescents	Cross-sectional. Survey  N = 6,700 junior high males N = 1,200 senior high males (southern California)	Tobacco Use (ST and cigarette)  Other drugs  Sports Participation  Psychosocial variables: Risk taking Self-esteem Perceived stress Susceptibility to peer influence	Trial use of a tobacco product: Trial use of both ST and cigarettes in junior high males associated with greater scores on risk-taking, perceived stress, susceptibility to peer influences, trial of alcohol, current use of alcohol, and trial of marijuana, and lower scores on self-esteem, relative to nontriers (p < 0.05)  Trial use of both ST and cigarettes in senior high males associated with greater scores on risk-taking, susceptibility to peer influences, trial of alcohol, current use of alcohol, relative to nontriers (p < 0.05)  Pattern was similar for monthly use.	<i>Strengths:</i> Large sample size  <i>Limitations:</i> Cross-sectional
(Tercyak & Audrain, 2002)	Psychosocial correlates of alternate tobacco product use during early adolescence	Cross-sectional. Survey  N = 1,123 9th grade students (Virginia)	Demographics  Cigarette smoking  Environmental  Smoking exposure  Depression  Alternate tobacco use	Alternative tobacco product use (OR, 95% CI): Current cigarette smoking: 17.1 (9.8-29.8) Exposure to others who smoke: 3.3 (1.6-7.0) Depressive symptoms: 2.0 (1.1-3.6)	<i>Strengths:</i> Examines both social and psychological correlates  <i>Limitations:</i> Cross-sectional Collapsed all alternate tobacco use- not just ST Low parental consent rates

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
<i>College Students</i>					
(Gottlieb, Cohen, & Haslam, 2014)	Comparing college smokers' and dual users' expectancies towards cigarette smoking	<p>Cross-sectional. Survey</p> <p>N = 306 undergraduate students  N = 140 dual users  N = 166 cigarettes</p> <p>(Southern U.S.)</p>	<p>Negative consequences</p> <p>Positive reinforcement</p> <p>Negative reinforcement</p> <p>Appetite-weight control</p>	<p>Dual users: &gt; white (<math>\chi^2 = 12.62</math>, <math>p = 0.05</math>) vs. other races, and male (<math>\chi^2 = 116.69</math>, <math>p &lt; 0.001</math>)</p> <p>Smoking expectancies relative to smokers: Smokers report greater positive reinforcement outcome expectancies compared to dual users (Mann-Whitney U = 9,894, <math>p = 0.988</math>, effect size, <math>\theta = 0.426</math>)*</p> <p>Dual users report greater negative consequences compared to smokers (U = 13,462.5, <math>p = 0.993</math>, <math>\theta = 0.579</math>)*</p> <p>Dual users report lower negative reinforcement expectancies (U = 9,316, <math>p = 0.001</math>, <math>\theta = 0.401</math>)  Dual users report lower weight/appetite reduction expectancies (U = 10,053, <math>p = 0.02</math>, <math>\theta = 0.433</math>)</p> <p>Smokers believe that smoking will lead to greater positive consequences when compared with their dual using counterparts.</p> <p>Dual users believe that smoking will lead to greater negative consequences.</p> <p>*Some inferences drawn by authors do not appear to align with statistical results.</p>	<p><i>Strengths:</i>  Representative sample of university population (female &gt; male)</p> <p><i>Limitations:</i>  Cross-sectional  No assessment of participants' reasons for being a dual user, nor amount of use of either product and history of use</p>

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
<b>Adults</b>					
(Cooper et al., 2010)	Differences between intermittent and light daily smokers in a population of U.S. military recruits	Population-based group randomized prevention and cessation trial (1-year follow-up)  N = 5,603 U.S. Air Force nondaily or light daily smoking recruits (U.S.)	Tobacco use history  Risk factors	Intermittent smoking (vs. daily smoking) Intermittent ST use: OR = 1.98 (95% CI: 1.41-2.79) (reference=never ST use) Daily ST use: OR = 5.39 (95% CI: 3.36-8.63) (reference = never ST use)  ST use may be associated with less smoking.	<i>Strengths:</i> Longitudinal  <i>Limitations:</i> Self-report Limited generalizability Frequency/ intensity of use not captured.
(Kalkhoran, Grana, Neilands, & Ling, 2015)	Dual use of smokeless tobacco or e-cigarettes with cigarettes and cessation	Cross-sectional. Survey  N = 1,324 adult smokers (U.S.)	Demographics  Tobacco use  Attitudes about ST use and risk perceptions	<u>Dual user demographics:</u> <i>Statistically significant associations:</i> There was an association between male sex (OR = 4.17; 95% CI: 1.65-10.53) and being a dual smokeless user compared to being a cigarette-only user. <i>Other demographics, not statistically significant:</i> Some college education: 36.07% 30-44 years old: 34.43% Southern U.S.: 45.9% Income < \$25,000: 39.34% Cigarettes per day, 11-20: 44.26% No difference between dual users and cigarette-only users on measures of education, age, geographical location, income, cigarettes/day  Predictors of dual use: Tried to quit by switching to ST (OR = 18.17; 95% CI: 8.59-38.40) Willingness to try ST when unable to smoke (OR = 1.32; 95% CI: 1.14-1.54)  ST use among smokers may be motivated by a desire to quit or when unable to smoke.	<i>Strengths:</i> Sample size  <i>Limitations:</i> Limited to current smokers-generalizability to former smokers Limited recall- unclear if use was experimental or regular Reporting bias

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Kasza et al., 2014)	Cigarette Smokers’ Use of Unconventional Tobacco products and associations with quitting activity: findings from the ITC-4 U.S. cohort	Longitudinal. Survey (International Tobacco Control Four Country Survey 2002–2011)  N = 6,110 adult smokers (U.S.)	Tobacco use  Use of ST  Perceptions of health risks  Other uses for products  Demographic	Use of ST: Chewing tobacco: 61% Moist snuff: 55% Nasal snuff: 5% Other: 9%  Male cigarette smokers more likely to use ST (OR = 6.03, 95% CI: 4.67–7.78, reference = females)  Younger (18-24 y = reference) more likely to use ST (OR range = 0.09-0.50 vs. other age groups) ”Other” ethnicity (reference) was more likely to use ST (OR = 0.59; 95% CI: 0.44-080)  ST use associated with higher scores on heaviness of smoking index (OR=1.51, 95% CI: 1.16–1.97).  53% of ST users use product to cut down on smoking.	<i>Strengths:</i> Longitudinal design Large, nationally representative sample size  <i>Limitations:</i> ~25% annual attrition; replaced yearly, but data from all years not available for many subjects. Low response rate (21%-35%), but characteristics of respondents similar to other benchmark surveys. Limited statistical power due to low rate of unconventional tobacco product use. Self-report – recall bias
(Klosky et al., 2013)	Smokeless and dual tobacco use among males surviving childhood cancer: a report from the Childhood Cancer Survivor Study	Cross-sectional. Survey (Childhood Cancer Survivor Study 2007)  N = 3,378 males (U.S.)	ST use (dependent variable)  Dual-use (dependent variable)  Demographics  Health Condition	ST users: 8.3% Dual tobacco users: 2.3%  Dual use significantly lower among cancer survivors (RR = 0.37; 95% CI: 0.29-0.46).  Dual use associated with: younger age at diagnosis (RR = 3.07, p = 0.002), non–college graduate (RR = 2.22, p = 0.03), separated/divorced (RR = 6.39, p < 0.0001), psychologically distressed (RR = 2.50, p = 0.048)  Dual use was independently associated with high psychological distress.	<i>Strengths:</i> Moderate sample size  <i>Limitations:</i> Possible underreporting Self-report Cross-sectional

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Kram et al., 2014)	Dual tobacco user subtypes in the U.S. Air Force: dependence, attitudes, and other correlates of use	Cross-sectional. Survey  N = 8,956 U.S. Air Force recruits (U.S.)	Demographics  Nicotine dependence  History of tobacco use  Future tobacco use intentions  Peer/household use  Attitudes  Athletic participation	<p>Compared with cigarette smoking, dual use (daily smokers/nondaily ST) associated with (OR, 95% CI):</p> <ul style="list-style-type: none"> <li>• Being male: 7.01 (2.78-17.70)</li> <li>• Expected to use ST in future: 22.2 (4.08-120.60)</li> <li>• &gt; 50% of friends use ST: 2.45 (1.20-5.01)</li> <li>• &gt; 50% of friends dual users: 4.55 (2.44-8.49)</li> <li>• Own items with tobacco advertising: 5.10 (1.11-23.40)</li> <li>• Played baseball in school: 2.95 (1 36-6.37)</li> </ul> <p>Compared with exclusive exclusive ST use, dual use (daily ST/nondaily smoking) associated with (OR, 95% CI):</p> <ul style="list-style-type: none"> <li>• Living in the Midwest: 2.60 (1.31-5.14)</li> <li>• Expected to use ST and other tobacco in future: 7.34 (2.20, 24.50)</li> <li>• &gt;50% of friends dual users: 2.17 (1.18-3.98)</li> <li>• &gt;50% of friends smoke: 3.61 (1.94-6.72)</li> <li>• Would consider using a product that claims to be safer than cigarettes: 2.92 (1.36-5.23)</li> </ul> <p>Compared with daily smoking/nondaily ST use, daily smoking/daily ST use associated with (OR, 95% CI):</p> <ul style="list-style-type: none"> <li>• Nicotine dependence: 2.72 (1.32-5.62)</li> <li>• Expected to use ST in the future: 2.84 (1 22-6.66)</li> </ul> <p>Compared with daily ST use/nondaily smoking, daily smoking/daily ST use associated with</p> <ul style="list-style-type: none"> <li>• Likely to use ST in future: ( OR = 0 16, 95% CI: 0.07-0.35)</li> <li>• Nicotine dependence: (OR = 2.84, 95% CI: 1.26-6.43)</li> <li>• &gt; 50% of friends smoke: (OR = 3.89, 95% CI: 1.56-9.68)</li> <li>• Likely to agree that ST is safer than cigarettes: (OR = 0.33, 95% CI:0.13-0.83).</li> </ul> <p>Risk factors for continued tobacco use increases if two products are being used concomitantly and if the frequency of use of the products is greater (i.e., daily vs. nondaily).</p>	<p><i>Strengths:</i> Large sample size</p> <p><i>Limitations:</i> Cross-sectional Limited generalizability to general population Self-report - recall bias</p>
(McClave-Regan & Berkowitz, 2011)	Smokers who are also using smokeless tobacco	Cross-sectional. Mail-in survey (2008)	Three groups: Smokers	Dual users: Men: 80.5%	<i>Strengths:</i> Large sample size



Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
	products in the U.S.: a national assessment of characteristics, behaviours and beliefs of 'dual users'	Consumer Styles survey)  N = 10,108 adults (U.S)	ST users Dual users  Demographics  Perceived harm  Use of ST when could not smoke	White: 75.7% 18-24 years: 34.5% Lower income < \$15,000: 25.9% South: 38.1% Use ST when they can’t smoke: 67.7% Do not believe ST will help with quitting smoking: 75.1% ST as harmful as cigarettes: 63.6% Do not know whether ST is as harmful as cigarettes: 22.7%  Dual users believed ST was as harmful to their health as cigarettes and were less likely than adults who use ST alone to believe ST is less harmful than cigarettes (OR = 0.21; 95% CI: 0.08-0.54).	<i>Limitations:</i> Mail-in survey Low response rate Low proportion of dual users Sample weighting to represent the U.S. population Inconsistency in reporting dual use prevalence in text (1.1 to 6.1%)
(O'Connor, Kozlowski, Flaherty, & Edwards, 2005)	Most smokeless tobacco use does not cause cigarette smoking: results from the 2000 National Household Survey on Drug Abuse	Cross-sectional. Survey (2000 National Household Survey on Drug Abuse)  N = 7,956 males aged 22–34 years (U.S.)	6 tobacco use categories  Lifetime tobacco status  Comparison to 1987 data	Nonsmokers more like to have never used ST (65.8%, 95% CI: 63.9-67.7) than former smokers (34.1%, 95% CI: 29.8-38.4) and current smokers (42.9%; 95% CI: 40.2-45.6) ( $\chi^2(4) = 300.2, p < 0.0001$ )  Among ST users: 21.7% (19.9-23.5) used cigarettes first 32.1% (30.1-34.1) used ST first	<i>Strengths:</i> Large sample size National sample, representative of population Comparison to results from 1987  <i>Limitations:</i> Little quantification of the levels of ST use by the participants Cross-sectional Self-report - recall bias
(Olmsted et al., 2011)	Overlap in use of different types of tobacco among active duty military personnel	Cross-sectional. Survey (2008 Department of Defense Survey)  N = 28,546 military personnel  (U.S.-based, includes worldwide U.S. military installations)	Past month use: Cigarette use ST use Cigar use	Risk for dual use (significant differences): 21-25 y (4.5%) and 26-34 y (4.1%) vs. 35 y (2.3%) Males (4.7%) vs. Females (0.6%) High school or less (4.6%), Some college (3.8%) vs. College graduate or higher (2.1%) Whites (5.7%) vs. “other (2.3%)” Not married (3.9%) vs. married, spouse present (3.4%)  Daily cigarette use in past month % (SE):	<i>Strengths:</i> Large sample size  <i>Limitations:</i> Uneven measures across tobacco types Self-report - recall bias Cross-sectional No data on ST users only

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
				Dual use: 59.6% (1.7) Cigarettes only: 65.9% (0.7)  1-5 cigarettes per day % (SE): Dual use: 35.1% (1.6) Cigarettes only: 30.9% (0.9)  6-10 cigarettes per day % (SE): Dual use: 33.1% (1.8) Cigarettes only: 38.8% (1.1)	
(Renner et al., 2013)	Tobacco use among southwestern Alaska Native people	Cross-sectional. Survey  N = 400 adult tobacco users (Alaska)	Demographics  Use  Amount used  Duration of use	Mean number of cigarettes per day was lower for dual users (5.7) than that for exclusive smokers (7.8; $p = 0.004$ ).  Dual users were more likely to both initiate (58.1%) and begin regular tobacco use (32.3%) at age 11 or younger compared with other groups (e.g., cigarette users: 38.7% and 10.4%, respectively).	<i>Limitations:</i> Limited generalizability to general population Inclusion of Iqmik in the dual user sample Self-report - recall bias Cross-sectional
(Brad Rodu & Cole, 2009)	Smokeless tobacco use among men in the United States, 2000 and 2005	Cross-sectional. Survey  N = 4.14 million ST users (2000)  N = 4.44 million ST users (2005)  (U.S.)	Tobacco use  Demographics  Social information	In 2005, there were more dual users aged 18-24 years than never smokers of the same age (34% vs. 14%, $p \leq 0.05$ ). No other significant differences among dual users with respect to demographic or social characteristics.  In 2000: Dual users smoked less vs. exclusive smokers (mean (SD): 13 (8) cigarettes/d vs. 20 (14) cigarettes/d, $p \leq 0.05$ ).  In 2005: Dual users smoked less vs. exclusive smokers (13 (7) cigarettes/d vs. 19 (14) cigarettes/d, $p \leq 0.05$ ).	<i>Strengths:</i> Large sample size  <i>Limitations:</i> Self-report - recall bias Cross-sectional
(Tomar, 2003)	Is use of smokeless tobacco a risk factor for cigarette smoking? The U.S. experience	Cross-sectional. Survey (1989 Teenage Attitudes and Practices Survey and 1993 follow-up)  N = 3,996 adolescent	Prevalence  Initiation  Quit rates  Switching	Baseline ST users, smoking at follow-up: Used ST regularly: OR = 3.45, 95% CI: 1.84-6.47 (reference = never use) Used ST, not regularly: OR = 2.01, 95% CI: 1.38–2.93 (reference = never ST user)  Baseline smokers, using ST at follow-up:	<i>Limitations:</i> Cross-sectional Differences in patterns of dual use due to birth cohort effects Self-report – recall bias

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
		males (11-19 y) (U.S.)		Current smokers: OR = 1.65, 95% CI: 0.32-8.52, not significant (reference = never smoker)	
(Tomar, Alpert, & Connolly, 2010)	Patterns of dual use of cigarettes and smokeless tobacco among U.S. males: findings from national surveys	Analysis of 4 cross-sectional surveys (TUS-CPS, MTF, the National Health and Nutrition Examination Survey, and the NYTS)  Adolescents and adults, sample sizes not reported (U.S.)	Frequency of use  Demographics  Sociodemographic	The prevalence of smoking was greater in adolescent ST users than nonusers.  Middle school: 69.1% of daily ST users smoked in the past 30 days 27.7% of daily smokers in the past 30 days also had used ST during that time period vs. 1.6% who had not smoked  High school: 60% of ST users smoked compared with 17% of those who did not use ST  In adults, daily dual users were younger than daily smokers (42.45 vs. 46.36 years, $p = 0.005$ ).	<i>Strengths:</i> Large sample size National survey data-geographic representation Cotinine-level data  <i>Limitations:</i> Cross-sectional designs Potential demographic differences between young people and adults that may influence future patterns of tobacco use Self-report – recall bias
(Trent, Hilton, & Melcer, 2007)	Premilitary tobacco use by male Marine Corps recruits	Cross-sectional. Survey  N = 15,689 male Marine Corps recruits (California)	Demographics  Tobacco use  Age of initiation  Amount used  Cravings  Quit attempts  Use by family/peers	26.1% use ST at least 20 times in lifetime 18.4% use 100+ cigarettes and 20+ ST (dual users)  Mean daily tobacco intake highest (~26 units per day using total tobacco intake/cigarette equivalents for ST calculation [TOTLTOTB]) in dual users compared with smokers (~12) and ST users (~21)	<i>Strengths:</i> Large sample size  <i>Limitations:</i> Cross-sectional Self-report – recall bias The authors attempted to calculate a “TOTLTOTB” values using nicotine equivalency assumptions that may or may not be valid. Limited generalizability
(Wetter et al., 2002)	Concomitant use of cigarettes and smokeless tobacco: prevalence, correlates, and predictors of tobacco cessation	Randomized, matched-pair design cancer prevention trial  N = 4,886 males	Prevalence  Baseline tobacco status	Approximately 4.5% dual users  Dual users were more likely to be: <ul style="list-style-type: none"> <li>• Younger</li> <li>• Unmarried</li> </ul>	<i>Strengths:</i> Prospective evaluation  <i>Limitations:</i> More dual users lost to follow-

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
		(southeastern U.S.)	Demographics  Environmental influences  Tobacco consumption  Smoking-related measures  ST-related measures  Abstinence Status	<ul style="list-style-type: none"> <li>• White</li> <li>• Have lower education levels</li> <li>• Consume more alcohol</li> <li>• Live with a smoker</li> <li>• Have worksites that do not prohibiting smoking completely</li> </ul> Dual users were similar to ST users with respect to age and ethnicity.	up vs. other groups Constrained by design of the larger Working Well Trial Focus on ST use and smoking separately vs. all tobacco use Self-report - recall bias
(S.-H. Zhu et al., 2009)	Quitting cigarettes completely or switching to smokeless: do U.S. data replicate the Swedish results?	Longitudinal study (1-year follow-up) using data from two TUS-CPS (2002 and 2003)  N = 15,056 adults (U.S.)	Tobacco user status	Tobacco user status change: Cigarette smokers to dual users: 2.2% (95% CI: 1.4-3.5) ST users to dual users: 1.8% (95% CI: 0.6-5.5) Dual users to exclusive smokers: 37.0% Dual users who remained dual users: 45.0%  Tobacco cessation at follow-up: Exclusive smokers: 11.6% ST users: 38.8% Dual users: 18% cigarettes and 50.1% ST	<i>Strengths:</i> Longitudinal Nationally representative sample

## **7.5.2-1.4. The Likelihood that Consumers Who May Have Otherwise Quit Using Tobacco Products Will Instead Use the Product**

### **7.5.2-1.4.1. Overview**

Section 7.5.2-1.4 focuses on cessation of tobacco product use in dual users, exclusive ST users, and exclusive cigarette smokers who switch to ST as a means of evaluating the likelihood that consumers who may have otherwise quit using tobacco products would instead use ST. Cigarette smoking represents the most common form of tobacco use in the U.S. and accounts for the majority of health risks; the assessment of those who use other combustible tobacco products (e.g., cigars, cigarillos) has not been included in the literature review due to limited published data on these other combustible tobacco products.

While there is no single study that prospectively examines the likelihood that consumers (“imminent quitters”) who may have otherwise quit using tobacco products (in this case cigarettes) will instead use ST, the literature supports that some cigarette smokers use ST to cut down on smoking, as an alternative to quitting tobacco altogether, and to help quit smoking (e.g. [\(Richardson et al., 2014\)](#)). Although use of ST appears to be a prevalent self-reported approach to altering smoking behaviors, there is no overall conclusive evidence to determine if ST use promotes or hinders cessation of smoking in the U.S. While some studies show a greater likelihood of cessation when using ST to quit (e.g., [\(K. Tilashalski, Rodu, & Cole, 1998; Ken Tilashalski, Rodu, & Cole, 2005\)](#) or attempting to quit [\(Messer et al., 2015; Tomar et al., 2010\)](#), other studies demonstrate no difference in cessation rates [\(Messer et al., 2015; Richardson et al., 2014; Wolfson et al., 2015; S.-H. Zhu et al., 2009\)](#).

### **7.5.2-1.4.2. Literature Review Results**

The literature search yielded 12 publications assessing the prevalence and correlates of smoking cessation behaviors in the context of ST use, in order to evaluate if ST use promotes or hinders cessation of smoking. Participants in these studies included mainly adults. Most participants were current or former smokers, and a smaller proportion were exclusive ST users or dual users (in this context, dual use is defined as using ST and cigarettes). The number of participants evaluated in these studies ranged from as few as 63 [\(K. Tilashalski et al., 1998; Ken Tilashalski et al., 2005\)](#) to as many as 67,293 [\(Tomar et al., 2010\)](#).

### **7.5.2-1.4.3. Longitudinal Studies**

Four longitudinal studies evaluated smokers’ or dual users’ use of ST products and its association with smoking cessation. Kasza et al. [\(2014\)](#) reported on the use of various tobacco products and reasons for using “unconventional” tobacco products (including ST) over a 9-year period (2002-2011) in a sample of 6,100 adult smokers. The authors also analyzed past-year quit attempts in relation to unconventional tobacco product use. Unconventional tobacco product use in adult smokers increased over the 9-year assessment period from approximately 10% to approximately 20%, but the prevalence of past-year ST use remained at approximately 5% or lower throughout the assessment period. In this study, 53% of ST users reported using ST to cut down on the amount of cigarettes smoked, 38% used ST as an alternative to quitting, and 43% reported ST use to help with quitting. While

there was a nonsignificant trend for ST use to be associated with a greater likelihood of attempting to quit smoking (OR = 1.25; 95% CI: 0.98-1.58), ST use was associated with a lower likelihood of quitting smoking than nonuse (OR = 0.57; 95% CI: 0.33-0.98). However, this study had a relatively high yearly dropout rate (25 %), which limited within-subject trajectories of tobacco product use and decreased statistical power due to the low rates of unconventional tobacco product use. Furthermore, there is the potential confound of having difficulty quitting (i.e., greater dependence on the choice to use an unconventional tobacco product), which was not accounted for in the study.

Wetter et al. (2002) evaluated the prevalence, correlates and predictors of tobacco cessation in male exclusive smokers (n = 936), exclusive ST users (n = 859), and dual users (n = 220). The authors reported that exclusive ST users were more likely to be abstinent (20 percent) than exclusive smokers (16 percent) and dual users (11 percent) at the 4-year follow-up. However, the likelihood of cessation varied as a function of amount of ST used and tobacco user type, with fewer ST uses per day associated with a greater likelihood of cessation in exclusive ST users (OR = 0.94, p = 0.01), and greater ST uses per day associated with cessation in dual users (OR = 1.15, p = 0.03).

Zhu et al. (2009) conducted a 1-year longitudinal survey in 2002-2003 to evaluate smoking cessation rates and ST switching patterns in 1,105 male smokers in the U.S. Based on this survey, 0.3% of baseline male smokers quit smoking and switched exclusively to ST, 2.2% became dual users, and 11.6% quit tobacco completely. In contrast, 3.9% of the 234 baseline male ST users quit ST and switched exclusively to cigarettes, 1.8% became dual users, and 35% quit tobacco completely. Furthermore, there was no significant association observed between ST use and smoking cessation rate in this study. While this study provided broad-scale population cessation rates, it did not indicate if ST assisted or hindered male smokers’ attempts to quit.

Wolfson et al. (2015) also evaluated the role of ST in smoking persistence/cessation in 274 male college students over a 4-year period. In that study, the majority of participants were exclusive smokers (67.2 percent) and 32.8 percent were dual users at baseline. Although the authors reported that baseline dual users were more likely to be smoking at the 4-year follow-up than baseline exclusive smokers, the effect was not statistically significant (adjusted OR = 1.30; 95 percent CI: 0.73-2.35).

#### **7.5.2-1.4.4. Cross-Sectional Studies**

Six cross-sectional studies evaluated smokers’ or dual users’ use of ST products and its association with smoking cessation. Popova et al. (Popova & Ling, 2013) conducted a national online survey of 1,836 current or recently former (< 2 years) adult smokers to evaluate the use of alternative tobacco product use on smoking cessation. Of these current or former smokers, approximately 13%-15% reported prior use of ST. Approximately 8% tried to quit smoking by using ST and another 5.8% had considered using ST to assist with quitting smoking, but had never tried. Of those who reported a past-year quit attempt, 8.9% reported switching to ST in order to quit smoking cigarettes. Of former smokers, 7.4% reported switching to ST to quit smoking. When participants were queried about use of ST in



the future, most indicated they were not open to it, but more open when the question was framed around the health risk reduction associated with quitting smoking.

Schauer et al. (2014) reported on the prevalence and correlates of switching to alternative tobacco products in an attempt to quit smoking in 12,400 current or former (quit attempt < 1 year) adult smokers. In this national online survey, participants were asked about past-year quit attempts, quit attempts by switching to ST or other combustible tobacco products and quit attempts using counseling or medications. Approximately 3.1 percent of participants reported switching to ST (vs. 2.2 percent switching to other combustible tobacco products), but the majority of participants indicated neither approach (94.2 percent). Being younger (18-24 years), male, white, a current someday smoker ( $\geq 100$  cigarettes in lifetime and currently smoking some days) and being less nicotine dependent (as assessed by TTFU >30 min) were associated with a higher likelihood of switching to ST to quit than no ST or use of other combustible tobacco products.

Tomar et al. (2010) reanalyzed data from the 2006-2007 Tobacco Use Supplement- Current Population Survey (TUS-CPS, 67,293 subjects) and reported that past-year quit attempts in adult male tobacco users were more prevalent among nondaily ST users/daily smokers (41.2 percent) than among daily exclusive smokers (non-ST users) (29.6 percent) and that these participants also showed a greater interest in quitting.

Richardson et al. (2014) observed that of 1,270 current smokers and 217 former smokers, approximately 21.1 percent reported use of ST to cut down on smoking and approximately 18.2 percent reported ST use to quit smoking; however, there was no statistically significant association between ST use and quit attempts. This finding is contrasted by Tilashalski et al. (1995), who reported that in former heavy smokers, switching to ST use was sustained with no self-reported relapse to cigarette use; however, this study was very small ( $n = 22$ ).

In a recent, large study of smokers, Messer et al. (2015) reported that current dual users ( $n = 675$ ) were 30 percent more likely to try to quit smoking than exclusive smokers ( $n = 26,760$ ). Approximately 48 percent of dual users reported use of ST to quit; however, quit rates (measured using past 30-day cessation) were not significantly different between exclusive smokers and dual users.

#### **7.5.2-1.4.5. Clinical Study**

Tilashalski et al. (K. Tilashalski et al., 1998; Ken Tilashalski et al., 2005) conducted a pilot study with a 7-year follow-up to evaluate the use of ST and a brief intervention (a lecture on health effects of tobacco use and use of ST as aid to quitting smoking) on smoking cessation in 63 adult smokers, the majority of whom had used NRT in past cessation attempts (termed “inveterate smokers”). The primary outcome was self-reported complete or partial ( $\geq 50\%$  reduction in number of daily cigarettes) past-month cessation at 3, 6, 9, and 12 months and again at 7 years. In the first year, 25% (31% males and 19% females; 16/63 total subjects) of smokers reported cessation by switching to ST. At 12 months, 4.8% of these participants (3/63) remained completely tobacco free, and 6.7% (4/63) reported partial smoking cessation. At 7 years, 44% (28/63) of the original sample had stopped smoking, and 15 of those 28 participants had used ST to quit. Of those 15 participants, 7 were tobacco free, and 8 continued to use ST. Of those participants who quit using ST at the 12-month follow-up,

75% (12/16) remained smoke free at 7 years. Of those who quit using a method other than ST (e.g., NRT, cold turkey), 67% remained smoke free. In contrast, 29% (12/41) of those still smoking at the 12-month follow-up were smoke free, with 3 participants reporting use of ST to quit. This study indicates that switching to ST may be a potential harm-reduction strategy, especially for smokers who have had difficulty quitting using other approaches (e.g., NRT) and that the long-term success rate (75%) in smoking cessation may be greater than that for other interventions. However, this study used a small sample size and did not include a control group to evaluate quitting behaviors in those not exposed to the ST/lecture intervention and how cessation rates directly compared with other interventions.

#### **7.5.2-1.4.6. Summary**

Due to the cross-sectional nature of several of the studies and attrition of study participants or short follow-up periods in the longitudinal studies, reliable long-term within-subject trajectories of tobacco product use are unavailable. Although there is some evidence that switching to ST is associated with greater cessation, overall, the current literature does not provide conclusive evidence to determine if ST use promotes or hinders cessation of smoking in the U.S.

Cigarette smokers cite use of ST to cut down on smoking, as an alternative to quitting tobacco altogether, and to help quit smoking. Thus, use of ST appears to be a prevalent self-reported approach to altering smoking behaviors with the aim of reducing health risks. While use of ST has been associated with a greater likelihood of quit attempts ([Messer et al., 2015](#); [Tomar et al., 2010](#)), cessation success appears to vary by level of nicotine dependence, user type (e.g., dual vs. exclusive user) and amount of ST consumed ([Messer et al., 2015](#); [Schauer et al., 2014](#); [Wetter et al., 2002](#)). [Table 7.5.2-1-4](#) presents a summary of the publications identified that assessed intercepting and quitting effects of ST.



**Table 7.5.2-1-4: Literature Evaluating Intercepting and Quitting Effects of Smokeless Tobacco**

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
<b>Longitudinal Studies</b>					
(Wolfson et al., 2015)	The role of smokeless tobacco use in smoking persistence among male college students	Longitudinal. Web-based survey  N = 274 male college students - smokers and dual users (North Carolina and Virginia)	Current cigarette smoking (past 30 days)  Current ST use (past 30 days)	Baseline: 67.2% exclusive smokers, 32.8% dual users.  Follow-up: baseline dual users 30% more likely to be current smokers than baseline cigarette smokers, but not statistically significant.  Results show trend that ST co-use may be associated with smoking persistence, although effect was not statistically significant.	<i>Strengths:</i> Longitudinal design  <i>Limitations:</i> Not nationally representative Amount of ST used in past month not quantified/categorized Level of nicotine dependence not captured Self-report - recall bias Limited statistical power
(Kasza et al., 2014)	Cigarette smokers’ use of unconventional tobacco products and associations with quitting activity: Findings from the ITC-4 U.S. cohort	Longitudinal. National cohort survey, 2002-2011 (telephone)  N = 6,110 adult smokers (U.S.)	Reasons for use of alternative tobacco products  Past-year quit attempts	53% report use of ST to cut down on amount smoked. 38% report use of ST as alternative to quitting. 43% report use of ST to help with quitting (vs. 25% of those who used other smoked tobacco products).  Intend to quit: OR = 0.83; 95% CI: 0.68-1.02 (reference = no intent to quit) Quit attempt: OR = 1.25; 95% CI: 0.98-1.58 (reference = nonuser) Cessation: OR = 0.57; 95% CI: 0.33-0.98 (reference = nonuser)  Across years, approximately 5% or fewer reported past-year use of chewing tobacco or snuff/snus.  The major reason reported for ST use was to cut down on amount smoked.  Nonsignificant trend for ST use to be associated with greater likelihood of quit attempt.  Unconventional tobacco product, including ST, use associated with lower likelihood of quitting smoking vs. nonuse.	<i>Strengths:</i> Longitudinal design Large, nationally representative sample size  <i>Limitations:</i> ~25% annual attrition; replaced yearly, but data from all years not available for many subjects. Low response rate (21%-35%), but characteristics of respondents similar to other benchmark surveys. Limited statistical power due to low rate of unconventional tobacco product use. Self-report – recall bias

(S.-H. Zhu et al., 2009)	Quitting cigarettes completely or switching to smokeless: Do U.S. data replicate the Swedish results?	Longitudinal. Nationally representative survey, 2002-2003  N = 15,056 adults (U.S.)	Smoking cessation rates  Switching to ST	Male smokers: 0.3% quit smoking and switched to ST. 2.2% became dual users. 11.3% quit completely (total: 11.6%).  Male ST users: 3.9% quit ST and switched to cigarettes. 1.8% became dual users. 35% quit completely (total: 38.8%).  No association between ST use and smoking cessation rate observed.	<i>Strengths:</i> Longitudinal design National sample  <i>Limitations:</i> Broad-scale population cessation rates, but study does not address if ST has helped male smokers quit smoking Limited 1-year follow-up to analyze switching behavior and assess annual cessation rates
(Wetter et al., 2002)	Concomitant use of cigarettes and smokeless tobacco: Prevalence, correlates, and predictors of tobacco cessation	Longitudinal. Multi-site study  N = 4,886 adult males (Southeastern U.S.)	Smoking/ST quit attempts  Abstinence status	Dual users had a higher mean (SD) number of smoking quit attempts in past year than smokers (3.8 [6.1] vs. 1.8 [4.4], $p < 0.001$ ).  Dual users least likely to quit using tobacco, ST users most likely to be abstinent: Cessation: 11% dual users, 16% smokers, 20% ST users.  Fewer cigarettes per day associated with greater likelihood of cessation in smokers (OR = 0.95, $p < 0.001$ ), but not dual users (OR = 1.0, $p = 0.92$ ).  ST uses per day inversely associated with cessation in ST users (OR = 0.94, $p = 0.01$ ).  ST uses per day positively associated with cessation in dual users (OR = 1.15, $p = 0.03$ ).  Nicotine dependence (e.g., as measured by number of cigarettes/d) predicted cessation in smokers and ST users, but not dual users.	<i>Strengths:</i> Prospective evaluation  <i>Limitations:</i> More dual users lost to follow-up vs. other groups Constrained by design of the larger Working Well Trial Focus on ST use and smoking separately vs. all tobacco use Self-report - recall bias

<i>Cross-Sectional Studies</i>					
(Messer et	Cigarette smoking	Cross-sectional.	Quit attempts (last	Dual users    Smokers	<i>Strengths:</i>

al., 2015)	cessation attempts among current U.S. smokers who also use smokeless tobacco	Survey  N = 26,760 smokers  N = 675 dual users (U.S.)	year)  30-day abstinence  Use of ST to quit	Quit attempts 44.7% 37.0% 30-day abstinence 11.7% 10.2% Use of ST to quit 48.0% N/A  Current dual users more likely to try to quit smoking (OR = 1.33; 95% CI: 1.15-1.53), with more dependent dual users more likely to attempt quitting than more dependent smokers.  Quit rates (30-day cessation) not different between exclusive smokers (11.7%; 95% CI: 9.5-13.8) and dual users (10.2%; 95% CI: 9.8-10.5).	Large, nationally representative sample  <i>Limitations:</i> Cross-sectional design Self-report - recall bias Small number of dual users
(Richardson et al., 2014)	Prevalence, harm perceptions, and reasons for using noncombustible tobacco products among current and former smokers	Cross-sectional survey  N = 1,270 current smokers  N = 217 former smokers (select cities in Alabama, Ohio, Arkansas, Texas, Missouri, Arizona, Pennsylvania, Oregon)	Use of ST to quit	21.1% reported ST use to cut down on cigarette smoking.  18.2% reported ST use to quit smoking.  No statistically significant association between use of ST and quit attempts, with exception of snus (OR = 2.92; 95% CI: 1.43-5.97).	<i>Strengths:</i> Large sample size  <i>Limitations:</i> Cross-sectional design Limited geographical generalizability Differential attrition across race/ethnicity, age and education Patterns of noncombustible tobacco product use not collected
(Schauer et al., 2014)	Prevalence and correlates of switching to another tobacco product to quit smoking cigarettes	Cross-sectional. National survey, 2010-2011 (household interview)  N = 12,400 current or former adult smokers (quit attempt <1 year)	Quit attempts: 1+ day over last 12 months  Quit by switching to ST or OCT  Quit using counseling or medications	Switch to ST: 3.1% Switch to OCT: 2.2% Switch to both ST and OCT: 0.6% Neither: 94.2%  More likely to switch to ST or OCT to quit if male and younger.  Current nondaily smoking and being white associated with switching to ST to quit.  Switching to other tobacco products is a prevalent self-reported approach to smoking cessation.	<i>Strengths:</i> Large sample size Nationally representative  <i>Limitations:</i> Did not evaluate complete switching or duration of switching attempt Cross-sectional design Self-report - recall bias No data on trajectory and sequence of tobacco use (dual or poly)

(Popova & Ling, 2013)	Alternative tobacco product use and smoking cessation: A national study	National cross-sectional survey, 2011 (online)  N = 1,836 current or recently (<2 years) former adult smokers (U.S.)	Use of alternative tobacco products  Quit status  Intention to Quit	ST-specific: Quit status: Successful quitters OR = 0.97 (never quitters = ref) Quit intentions: Quit next month (OR = 0.79), quit in next 6 months (OR = 1.16) and quit in future but not in next 6 months (OR = 1.0) (never expect to quit = ref)  Any alternative tobacco product use: Quit status: OR = 0.68-1.78 (p<0.05) Quit intentions: OR = 0.26-1.62 (next month), 0.68-2.48 (> 6 months), 1.00-1.71* (within 6 months)  ~13%-15% reported use of ST.  Alternative tobacco product use to quit smoking: 7.8% tried quitting by using ST. 5.8% reported considering ST products to quit, but never tried.  Past-year quit attempts: 8.9% reported switching to ST to quit smoking. Of former smokers, 7.4% reported switching to ST to quit smoking.  Most subjects were not open to using ST in the future in general, but more open when question framed around health risk reduction/quitting.	Nationally representative sample  Cross-sectional - cannot determine direction of association between use and cessation attempts, nor if use facilitates quitting or leads to successful quitting Self-report- recall bias Limited to current and former smokers
(Tomar et al., 2010)	Patterns of dual use of cigarettes and smokeless tobacco among U.S. males: findings from national surveys	Analysis of 4 national cross-sectional surveys, 1999-2006  NYTS: N = 12,766  TUS-CPS: N = 67,293  NHANES: N = 826  MTF: Not reported	Interest and attempts to quit smoking	Past-year quit attempts more prevalent among nondaily ST users (41.2%) vs. daily smokers/non-ST users (29.6%) and greater interest in quitting.  Authors suggest that early dual use may be associated with higher likelihood of cigarette smoking later in life (see limitations of such inference).  Authors suggest that nondaily ST users/daily smokers more likely to have unsuccessful quit attempts, but show higher interest in quitting smoking (see limitations).	Large nationally representative sample Use of multiple data sources  All surveys cross-sectional; therefore, limited ability to examine patterns of transition in tobacco product use. “Differences in patterns of tobacco use among adults may differ as today’s your people progress through life.” Limitation in interpreting less success in quitting smoking among nondaily ST users due to

					cross-sectional nature of surveys. Self-report - recall bias
(K. Tilashalski et al., 1995)	Modified tobacco use as a risk-reduction strategy	Cross-sectional survey (Alabama)  N = 22 ST users/former smokers	ST transition and use	Switch mainly related to health risks/smoking-related illness.  13/22 switched directly to ST.  9/22 had tried "cold turkey"; 6 switched to ST after a period of tobacco abstinence and 3 reinitiated smoking before switching to ST.  No reports of relapse after switching.  In this small sample of former heavy smokers, switching to ST use was motivated by health reasons and was sustained with no self-reported relapse to cigarette use.’	Cross-sectional design; small number of participants, limited generalizability, not followed to evaluate complete tobacco abstinence Self-report - recall bias
<b>Clinical Studies</b>					
(K. Tilashalski et al., 1998)	A pilot study of smokeless tobacco in smoking cessation	Pilot clinical study of short behavioral intervention and using ST as quit aid (Skoal Bandits)  N = 63 adult smokers	Complete cessation (self-reported, past month) or partial cessation (50%+ reduction in daily cigarettes) at 3, 6, 9 and 12 months	Cessation by switching to ST: 31% males and 19% females (average: 25%). 3 completely abstinent from all tobacco at 12 months, confirmed by CO. Partial cessation by switching to ST: 6.7% at 12 months  Switching to ST may be a potential harm-reduction strategy, particularly for smokers who have had difficulty quitting using other approaches (e.g., NRT).	Longitudinal design allowed for follow-up to 1 year  Small sample size No control group
(Ken Tilashalski et al., 2005)	Seven year follow-up of smoking cessation with smokeless tobacco	Follow-up to pilot study  N = 63 original N = 58 follow-up	Complete cessation (self-reported)  CO in expired air	44% (28/63) ceased smoking; 15 of these used ST to quit (7 tobacco free and 8 using ST).  Of those who quit at 12 months using ST, 75% remained smoke free at 7 years (12/16).	7 year follow-up period allowed assessment of long-term success of ST use as smoking cessation strategy  Small sample size

				<p>Of those who quit using method other than ST, 67% remained smoke free at 7 years (4/6).</p> <p>Of those still smoking at 12 months, 29% (12) were smoke-free, with 3 reporting use of ST to quit.</p> <p>Long-term success rate of ST use as strategy to quit smoking compares favorably with that in other intervention studies (e.g., 75% vs. 7% for NRT).</p>	<p>No control group (but there was comparison with those who continued smoking in this cohort)</p>
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### **7.5.2-1.5.The Likelihood that Consumers Will Use the Product as Intended or Designed**

#### **7.5.2-1.5.1. Overview**

ST is a consumer product without specific directions for use or application; therefore, the likelihood that consumers will or will not use the product as intended or designed cannot be effectively assessed. However, the topography of ST consumption has been reviewed thoroughly in the literature and is summarized in [Section 7.5.8-1](#) and [Section 7.5.8-2](#) of this MRTPA. Briefly, the available published literature indicates the “average” user of ST uses about 7 to 8 dips per day and 3 to 4 cans per week. An average dip size is between 1 to 2 g. A typical dip lasts about 40 to 50 minutes, and over an entire day, a user keeps dip in their mouth for approximately 5 to 6 hours. This average topographical pattern of ST use approximates that reported for subjects permitted to use *ad libitum* (average: 15.6 g/d) in [Benowitz et al. \(1989\)](#), resulting in average blood nicotine concentrations comparable to those observed when the same subjects were permitted to smoke *ad libitum* in that study (36.4 cigarettes per day; see [Section 7.5.2-1.6.5.1](#)).

### **7.5.2-1.6.The Abuse Potential and the Potential for Misuse of the Product as Compared to Other Tobacco Products on the Market**

#### **7.5.2-1.6.1. Overview**

As nicotine is considered to be the primary pharmacological determinant of tobacco’s abuse potential, our approach for addressing abuse potential of ST focuses on the rate and extent of nicotine delivery and resulting behavioral-psychological effects as contributing to the likelihood for sustaining patterns of use (reinforcing effects). A major recommendation made by leading experts in abuse potential was that results of abuse potential assessments should be integrated and evaluated so as to more accurately predict risk of initiation, dependence, and persistence of use ([J. E. Henningfield, Hatsukami, Zeller, & Peters, 2011](#)). Since ST products have been available for decades, there is significant information already available about these topics. In this MRTPA, a summary of such direct measures of initiation, dependence potential and use behavior, based on national surveys, is provided in earlier sections and in [Section 7.5.3-1](#) and [Section 7.5.3-2](#). In addition, we summarize the literature on the abuse potential of ST products as compared with that for conventional cigarettes and NRT (as available).

The literature review related to the abuse potential of ST is divided into the following categories:

1. Misuse and abuse of ST ([Section 7.5.2-1.6.3](#))
2. Initiation of use of ST ([Section 7.5.2-1.6.4](#))
3. PK and PD effects of ST and its withdrawal ([Section 7.5.2-1.6.5](#))
4. Dependence on ST ([Section 7.5.2-1.6.6](#))

5. Cessation of ST ([Section 7.5.2-1.6.7](#))

6. Nonclinical abuse potential of ST and its extracts ([Section 7.5.2-1.6.8](#))

The following key points summarize the literature-based evidence on the relative abuse potential of ST:

- The limited number of reports in the literature supports that misuse and abuse of tobacco products, including ST, is very rare.
- Although several nonpharmacological factors contribute to tobacco use initiation (e.g., availability, peer influences), initiation of ST use is consistently and significantly lower than that of cigarettes, supporting that the intrinsic reinforcing efficacy is lower for ST.
- Controlled clinical trials show notable differences in subjective effects (e.g., satisfaction, liking, and craving) between ST and cigarettes, supporting that ST has significantly lower abuse potential than cigarettes, although greater than that for NRT. Such differences in PD effects are congruent with the lower rate of nicotine exposure with ST when compared with that for cigarettes.
- ST suppresses withdrawal and craving less effectively than cigarettes. Similarly, withdrawal signs and symptoms in ST users are similar to those reported in smokers, but the magnitude of withdrawal appears to be lower in ST users.
- Studies show that dependence may be similar or lower in ST users as compared with that in cigarette smokers; however, overall cessation rates appear to be higher in ST users than in cigarette smokers, suggesting a lower dependence potential.
- Based on available nonclinical studies, nicotine content appears to be the primary pharmacological determinant of the abuse potential of ST products.

Overall, the available evidence suggests that the abuse potential of ST is higher or similar to that of NRT, but consistently lower than that of cigarettes.

#### **7.5.2-1.6.2. Literature Review Results**

After the initial literature, additional publications were identified through review of the reference lists within the identified publications. Additional, specific searches were conducted to identify publications and national survey data on cigarettes in order to make relative comparisons with tobacco smoking. The literature search yielded a total of 54 publications used to inform the abuse potential and potential misuse of the product compared to other tobacco products on the market.

#### **7.5.2-1.6.3. Misuse and Abuse of ST**

Very little literature exists on the misuse and abuse of ST, in part because of the nature of the product. For pharmaceutical products, misuse refers to using a drug in excessive quantities or using a drug for purposes for which it was not intended ([World Health Organization, 1994](#)). Abuse refers to the “maladaptive pattern of drug use leading to clinically significant impairment or distress, such as recurrent substance use in physically hazardous situations,



and continued use despite persistent or recurrent social/interpersonal problems caused by the effects of the drug” ([American Psychiatric Association, 2000](#)). These criteria do not apply to a tobacco product. Unlike a pharmaceutical product, ST is a consumer product with no specific directions for use. For the purpose of this program, we characterized misuse/abuse of ST as any use outside of “normal use,” which is placement of the manufactured product in the oral cavity.

Within the current literature, a case report was identified in which a 49-year-old woman used dry snuff to brush her teeth for up to 9 hours per day, using 5 to 6 tins per day (approximately 1.4 g snuff/tooth brushing session), for a period of approximately 12 years ([Edwards, 1987](#)). The patient could not identify the reason for using the product in this manner, but analyses confirmed that plasma nicotine levels were within the range achieved by heavy smokers. Other cases of tobacco misuse include making concentrated extracts of tobacco to be used as folk remedies for various health conditions ([Garcia-Estrada & Fishman, 1977](#); [O’Berst & McIntyre, 1953](#); [Willis, 1937](#)) or intentionally attempting to commit suicide by ingesting the concentrated extract ([Schneider et al., 2010](#)). In the cases described above, the source of the tobacco (i.e., smoking tobacco or ST) is not readily discernible from the reports, and thus the misuse cannot be attributed to a particular product. However, the paucity of reports suggests that misuse and abuse are historically quite rare for tobacco products in general, including ST products.

#### **7.5.2-1.6.4. Initiation of Use of ST**

Initiation of ST use is described in detail in [Section 7.5.2-1.1](#) (current tobacco users) and [Section 7.5.3-1](#) and [Section 7.5.3-2](#) (nonusers); however, the uptake of tobacco product use is in part related to the reinforcing effects of the product. As such, this section briefly describes relative initiation rates and initial response as one potential proxy measure of the relative abuse potential of ST as compared with that of cigarettes.

Data from the NSDUH ([Substance Abuse and Mental Health Services Administration \[SAMHSA\], 2013](#)) show that the estimated yearly number of individuals 12 years of age or older who initiated use of cigarettes was higher than that for those who initiated ST between 2002 and 2012. Results of [Chisick et al. \(1992\)](#) support that a greater proportion of adolescents (n = 2,231) tried cigarettes only (27.7 percent) than the proportion that tried ST only (3.2 percent). However, 13.2% of these adolescents have tried both cigarettes and ST. Therefore, the total percentages of adolescents who have tried cigarettes and ST were 40.9% and 16.4%, respectively.

Initiation of both ST use and cigarette smoking primarily occurs before age 18 years. For example, the 2012 NSDUH demonstrated that 51.4% of new smokers and 46.3% of new ST users were less than 18 years of age. In 2012, the average age of first cigarette use was 17.8 years, and the average age of first ST use was 18.8 years ([Substance Abuse and Mental Health Services Administration \[SAMHSA\], 2013](#)). While age at initiation peaks in adolescence for both smoking and ST use, survival analyses showed that the risk of initiating ST use extends into adulthood ([Howard-Pitney & Winkleby, 2002](#)).

Several nonpharmacological factors contribute to initiation of tobacco use and appear to be common across tobacco products. For example, [Holman et al. \(2013\)](#) observed that peer

influence, rebelliousness, and thrill-seeking were strongly predictive of ST initiation in young male adolescents, which is similar to predictors of initiating smoking during adolescence (Bricker et al., 2009; Otten, Bricker, Liu, Comstock, & Peterson, 2011).

Initial response to ST is similar to that of cigarettes, suggesting that the effects experienced are primarily related to the psychoactive substance, nicotine. For example, commonly reported effects of first ST use include general negative effects, feeling sick, and dizziness, which is consistent with the literature on cigarettes (Ary et al., 1989; Eissenberg & Balster, 2000). Increased sensitivity to these effects of nicotine, be they positive (“buzz” or dizziness) or negative (nausea), has been shown to influence the likelihood of continued cigarette use (J. R. DiFranza et al., 2004; O. F. Pomerleau, Collins, Shiffman, & Pomerleau, 1993). However, the relationship between initial response and continued use of ST has not been well investigated (i.e., only a single study with Swedish snus) (Zabor et al., 2013). To the best of our knowledge, no other studies have specifically evaluated the initial response to ST and subsequent use.

Overall, the available evidence on initiation supports that the abuse potential of ST is lower than that of cigarettes, although it is acknowledged that nonpharmacological factors play an important role in relative rates of initiation.

#### **7.5.2-1.6.5. Pharmacokinetic and Pharmacodynamic Effects of ST and Its Withdrawal**

The speed of delivery of drugs to the central nervous system can have a significant impact on their reinforcing effects (e.g., (Abreu, Bigelow, Fleisher, & Walsh, 2001; de Wit, Bodker, & Ambre, 1992; de Wit, Dudish, & Ambre, 1993)). Thus, the observed differences in rate of nicotine delivery from various tobacco- and nicotine-containing products can influence their relative abuse potential. In addition to *speed* of delivery, the substantial differences in peak (maximum measured concentration [ $C_{max}$ ]) and overall exposure (area under the concentration–time curve [AUC]) to nicotine after administration of cigarettes, ST products, and NRT are some of the important factors that may contribute to their relative abuse potential. For example, several NRT products exhibit slower kinetics and are associated with significantly lower abuse potential than that with cigarettes (K. Fagerstrom & Eissenberg, 2012). However, the relationship between exposure and subjective response appears to be complex, and may follow an inverted U-shaped curve, with higher exposure potentially associated with lower liking due to emergence of negative effects (e.g., nausea, anxiety (Fant, Henningfield, Nelson, & Pickworth, 1999)).

The following sections summarize the published literature on the PK (Section 7.5.2-1.6.5.1) and PD effects of ST after acute and repeated administration (Section 7.5.2-1.6.5.2) and after its withdrawal (Section 7.5.2-1.6.5.3), and where available, comparisons relative to other nicotine-containing products, such as cigarettes and NRT, are made. Section 7.5.2-1.6.5.4 summarizes the available literature on nicotine dose-response of MST.

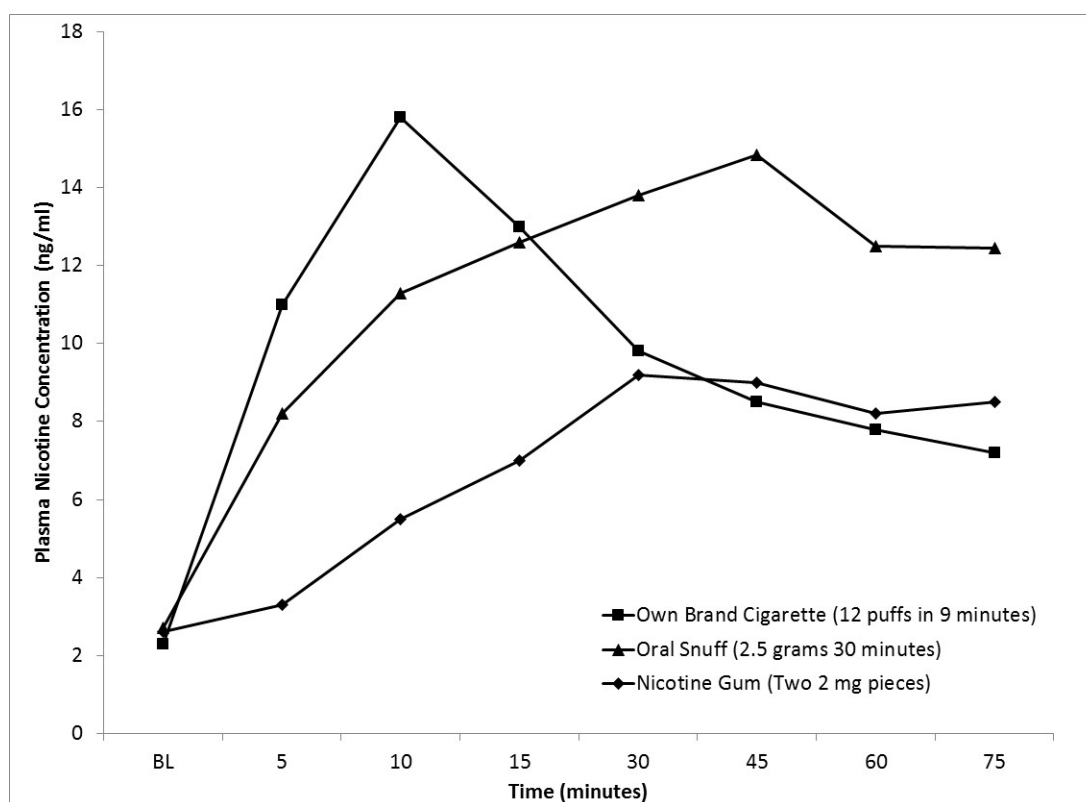
##### **7.5.2-1.6.5.1. Pharmacokinetics of Nicotine in ST**

Studies evaluating the PK of ST were generally conducted using a randomized crossover design in tobacco users under controlled laboratory conditions, with product administration occurring after a prespecified period of abstinence (3-12 hours, depending on the study). In

several of the studies, PD responses were also collected; the results of these PD studies are more fully summarized in [Section 7.5.2-1.6.5.2](#).

The PK profile of nicotine varies substantially across tobacco and nicotine products, and also shows notable interindividual variability. In a review conducted by [Benowitz et al. \(1997\)](#), the authors summarize the results of several studies evaluating the PK profile of ST and contrast it with those of cigarettes and NRT. As seen in Figure 7.5.2-1-2, absorption and delivery of nicotine from ST products (e.g., oral snuff, chewing tobacco) are relatively slow, with  $C_{max}$  typically occurring within 30 minutes ([Benowitz, Porchet, Sheiner, & Jacob III, 1988](#); [Cobb, Weaver, & Eissenberg, 2010](#); [Fant et al., 1999](#)), whereas cigarette smoking provides a bolus dose of nicotine within 5-7 seconds of an initial puff, and  $C_{max}$  is achieved within 5 minutes ([Benowitz et al., 1988](#); [Berridge et al., 2010](#); [Cobb et al., 2010](#); [Vansickel, Cobb, Weaver, & Eissenberg, 2010](#)). The absorption profile of oral NRT (e.g., gum) is more similar to that of ST, but overall exposure may be lower with NRT, although this is highly variable between different ST products ([Cobb et al., 2010](#); [Fant et al., 1999](#)).

**Figure 7.5.2-1-2: Blood Nicotine Concentration Over Time After Single Administration of a Cigarette, Smokeless Tobacco (Oral Snuff) and Nicotine Polacrilex Gum**

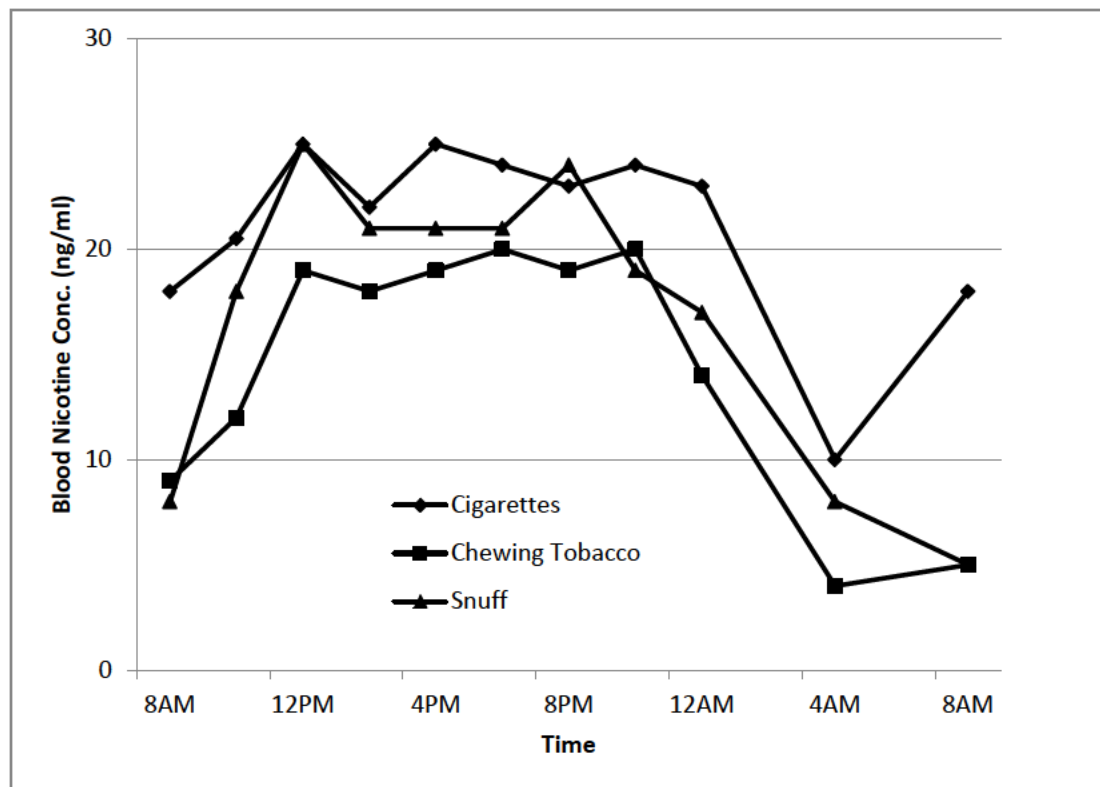


Source: Data replotted from Benowitz et al. ([Benowitz et al., 1988](#))  
 Oral snuff = Copenhagen® or Hawken-Wintergreen.

Nicotine exposure, as measured by AUC, from ST products is generally higher than that from NRT and cigarette smoking after acute administration (e.g., ([Benowitz et al., 1988](#); [Fant et al., 1999](#); [Kotlyar et al., 2007](#))); however, [Cobb et al. \(2010\)](#) reported significantly lower nicotine

exposure following administration of pouch ST (i.e., Camel® snus, Marlboro® snus) compared with cigarette smoking. While generally higher following acute administration, steady-state nicotine levels may be similar to those reported in heavy smokers when users are permitted to smoke or use ST *ad libitum* throughout the day (Figure 7.5.2-1-3) (Benowitz, 1997)).

**Figure 7.5.2-1-3: Blood Nicotine Concentration Over Time During *Ad Libitum* Administration of Cigarettes and Smokeless Tobacco**



Source: Data replotted from Benowitz et al. (Benowitz et al., 1989).

Oral snuff = Copenhagen® (n=5), Skoal Bandits Wintergreen (n=2), Hawken Wintergreen (n=1)

Average use: snuff = 15.6 g/d, chewing tobacco = 72.9 g/d, and smoking = 36.4 cigarettes per day.

Several factors contribute to the observed PK profile of nicotine after acute ST use as compared with that after cigarette smoking. First, cigarette smoking delivers nicotine to arterial blood via the pulmonary alveoli, whereas nicotine from ST is absorbed through the buccal mucosa (and gastrointestinal tract through swallowing) into venous blood and is subject to first-pass metabolism when swallowed (Benowitz, 1997; J. E. Henningfield, London, & Benowitz, 1990; J. E. Henningfield, Stapleton, Benowitz, Grayson, & London, 1993). Second, bioavailability of nicotine from ST is highly dependent on the nicotine concentration, pH level, and type of ST product (J.E. Henningfield, Radzius, & Cone, 1995), as well as on the user’s characteristics, including salivary pH and mucosal characteristics. Buccal absorption of nicotine appears to be impacted by pH of the surrounding milieu, with nicotine crossing the mucosal barrier more readily at higher pH levels in its unionized form (Beckett, Gorrod, & Jenner, 1972; Fant et al., 1999). These factors may help explain the

considerable variation in exposure across individuals, even when controlling for dose and timing of ST administration (Benowitz et al., 1988; Fant et al., 1999; Gritz, Baer-Weiss, Benowitz, Van, & Jarvik, 1981).

#### 7.5.2-1.6.5.2. Subjective Effects of ST

Section 7.5.2-1.6.5.2 summarizes the literature on the subjective effects of ST and where available, as compared with cigarettes and NRT. The identified studies were generally conducted using a randomized crossover design, with acute product administration occurring after a prespecified period of abstinence (3-12 hours, depending on the study). The specific scales and questionnaires varied by study; the measures included subjective assessments of direct effects of nicotine/tobacco (e.g., 100-point visual analog scales), craving and withdrawal (e.g., Hughes-Hatsukami questionnaire (Hughes & Hatsukami, 1986)), administered at prespecified time points after administration of the products. In each study, plasma nicotine concentrations were also determined.

Cobb et al. (2010) evaluated the PK and subjective effects (withdrawal, craving, direct effects [e.g., pleasantness]) of oral noncombustible nicotine/tobacco products relative to cigarettes (own brand) in 28 current smokers. In this randomized crossover study, the subject’s own brand cigarettes yielded the highest plasma nicotine concentrations when compared with those for all noncombustible products (Camel snus, Marlboro snus, Ariva® tobacco tablet, Commit® nicotine lozenge). Some noncombustible products significantly decreased craving (Marlboro snus, Camel snus, Commit nicotine lozenge) and withdrawal (Camel snus, Commit nicotine lozenge) at some of the assessment time points relative to baseline, but effects were significantly lower than those for cigarettes ( $p < 0.05$ ). The noncombustible tobacco products were associated with increased ratings of pleasantness relative to baseline, but pleasantness scores were significantly lower for the noncombustible tobacco products than those for cigarettes ( $p < 0.05$ ); the Commit nicotine lozenge did not significantly increase ratings of pleasantness relative to baseline. Thus, based on this acute exposure assessment, noncombustible products may suppress some withdrawal and craving effects, and the noncombustible tobacco products may elicit some positive effects. However, the effects of the noncombustible tobacco products were significantly lower than those for cigarettes.

Kotlyar et al. (2007) compared the PK and subjective effects of loose ST (Copenhagen®, no additional product description was provided) with lower-nicotine-content ST (Ariva and Stonewall® tobacco tablets and Revel® ST pouch) and NRT (Commit 4 mg nicotine lozenge) in 10 ST users. Nicotine  $C_{max}$  and AUC were significantly higher for Copenhagen® ST (16.1 ng/mL and 1038 ng×min/mL, respectively) than for the other products (2.6 to 7.3 ng/mL and 189 to 467 ng×min/mL, respectively  $p < 0.002$ ). Copenhagen® ST administration also resulted in significantly lower craving scores and in significantly higher scores on scales measuring good effects, satisfaction, liking, desirability, and strength than those for NRT and for lower-nicotine-content ST products ( $p < 0.05$ ). Additionally, withdrawal symptoms during use of Copenhagen® were significantly lower than during the use of Revel ( $p = 0.009$ ).



The nicotine PK and PD of ST can vary substantially across products. Fant et al. (Fant et al., 1999) studied the PK and PD of ST products varying in nicotine and pH content in 10 male ST users using a randomized crossover design. Copenhagen® loose ST administration resulted in the highest peak ( $C_{max}$ ) and overall (AUC) exposure as compared with the  $C_{max}$  and AUC of other ST products (i.e., Skoal Long Cut Cherry loose ST, Skoal Original Wintergreen ST, Skoal Bandits pouch ST). The authors also reported an exposure-dependent increase in subjective effects of ST (e.g., strength, nausea, heart racing, anxious); however, there was no dose response on measures of liking or craving. Despite the large differences in nicotine plasma levels, there were minimal differences in “craving” scores that were not statistically significantly different. These observations suggest that nicotine PK appears to play a minimal role in the reinforcing effects of ST products. Limitations of this study include the potential confounding effect of subjects’ brand of choice (most subjects typically used Copenhagen®), the lack of evaluation of overall response to the products, and the relatively small sample size.

Gritz et al. (1981) evaluated plasma nicotine and cotinine concentrations, as well as subjective effects following administration of *ad libitum* ST in 12 male ST users. The authors observed that nicotine and cotinine concentrations did not correlate with tobacco consumption on test day (or with self-reported consumption), and few subjective effects were reported, although large changes in nicotine/cotinine concentrations (from morning to afternoon) were associated with significant decreases in subject-rated relaxation/satisfaction and increase in subject-rated stimulation ( $p < 0.05$ ).

Coffey and Lombardo (1998) evaluated the effect of varying nicotine content on urges to use ST in 24 male ST users in a randomized crossover design. Products administered included 0% ST (non-nicotine-containing ST), 50% ST (half of ST content contained nicotine), 100% ST (own brand), and no ST. Independent of nicotine content, the urge for ST decreased after administration of the products ( $p < 0.01$ ). These results suggest that sensory and behavioral cues (e.g., handling ST tin, placing a dip in the mouth) contribute significantly to subjective responses to ST administration. Ratings of liking were significantly higher for the 100% ST condition, but did not differ between the 0% and 50% ST conditions; a similar pattern of effects was observed for other measures, including satisfaction, and sensory ratings of strength and “nicotine.” This study was limited as it did not contain a control for general oral stimulation and assessed subjective ratings at only a single time point.

Further to clinical laboratory assessments of the subjective effects and PK of various tobacco products, randomized crossover “actual use” studies have evaluated the effect of ST products on withdrawal symptom suppression, direct effects of nicotine, and amount of product use over 5-day outpatient sampling periods. To date, no studies have specifically included MST; however, results of studies evaluating U.S. snus and other noncombustible tobacco products indicate that, while nicotine is an important factor in suppressing withdrawal and craving, it is not the sole determinant of use.

Blank and Eissenberg (2010) reported that relative to own brand cigarettes, ST products (Ariva tobacco tablet and Camel snus) were associated with less withdrawal symptom suppression, greater craving and lower subjective ratings of liking and satisfaction in 21

cigarette smokers. As was consistent with these findings, participants used significantly less ST than cigarettes and had lower urine cotinine concentrations.

Hatsukami et al. (2011) evaluated preference and effects of ST products (pouch and lozenge) of varying nicotine content (relative nicotine content: General® snus>Camel snus>Marlboro snus>Stonewall tablet>Ariva tablet) in 99 cigarette smokers who were interested in quitting. After a sampling period, subjects were to choose a product for a 2-week cigarette-abstinence phase. Although highest in nicotine content, General snus was not chosen for the cigarette abstinence phase, and all other products were selected by a similar proportion of subjects, regardless of nicotine content, supporting that nicotine content alone is not indicative of product preference. However, Camel snus (highest nicotine content of the chosen products) was associated with greater relief of craving, greater satisfaction, reduced use of cigarettes, and greater abstinence when compared with what was reported by Marlboro snus and lozenges, although no differences were observed in withdrawal scores. Subsequent analysis of the relationship between subjective responses and extent of product use revealed that satisfaction was the only significant predictor of product *consumption*, although other measures (e.g., relief, psychological reward) were also associated with product *choice* (D. Hatsukami, Zhang, O'Connor, & Severson, 2013).

#### 7.5.2-1.6.5.3. Subjective Effects of ST Withdrawal

Continued use of tobacco products may in part be related to alleviation of nicotine withdrawal symptoms and craving (Benowitz, 2010). The subjective effects of ST withdrawal have been examined in the four clinical laboratory studies summarized below. Measures varied by study, but most used the Withdrawal Symptom Checklist (a 12-item checklist using Likert scale (Hughes & Hatsukami, 1986)).

Hatsukami et al. have conducted several studies evaluating the subjective effects of ST withdrawal. Hatsukami et al. (D. Hatsukami, Anton, Keenan, & Callies, 1992) evaluated ST abstinence symptoms and the effect of nicotine gum in 80 male Copenhagen® ST users using a randomized parallel group design. Abstinence from ST resulted in increased craving, difficulty concentrating, restlessness, hunger, increased eating, and increased total withdrawal scores (self-rated and observer-rated), as well as increased reaction time. Administration of nicotine-containing gum (0, 2, 4 mg) during the abstinence period increased cotinine levels in a dose-dependent manner. However, there were no nicotine gum dose-dependent differences seen in the severity of withdrawal symptoms, including craving and total withdrawal score, except in subjects with high baseline cotinine levels. The authors reported that total withdrawal scores were lower than those reported by cigarette smokers in previous studies, and fewer withdrawal symptoms were experienced (e.g., absence of anxiety and irritability). The lack of dose response on withdrawal symptom suppression with NRT administration could have been related to a strong placebo effect (oral stimulation) or milder withdrawal symptoms in ST users.

Hatsukami et al. (D. Hatsukami, Gust, & Keenan, 1987) compared withdrawal symptomatology in 16 Copenhagen® ST users and 11 cigarette smokers. During the abstinence period, both ST users and cigarette smokers reported increased craving, confusion, sleep disturbances (increased awakenings), and total scores on the Withdrawal

Symptom Checklist; however, only cigarette smokers reported increased anger/hostility and tension/anxiety, as well as decreased vigor (measured using Profile of Mood States). Overall, effects were generally greater in smokers than in ST users, as seen by higher scores on the Withdrawal Symptom Checklist and Profile of Mood States tension/anxiety, depression/dejection, and anger/hostility subscales, despite similar baseline cotinine levels (proxy for nicotine intake). A differential period of abstinence (3 days for ST users and 5 days for cigarette smokers) may have confounded the results, although only the first 3 days were included in the analysis.

[McChargue and Collins \(1998\)](#) evaluated withdrawal signs and symptoms using the Withdrawal Symptom Checklist and select Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision ([American Psychiatric Association, 2000](#)), criteria for nicotine withdrawal severity in both smokers (approximately 13.9 cigarettes per day) and male ST users (approximately 2.9 tins/week; approximately 4.7 dips per day). Both groups experienced withdrawal and craving after 48 hours of deprivation; however, there were no group differences in magnitude in this study.

In another study, [McChargue et al. \(2002\)](#) used the Minnesota Nicotine Withdrawal scale to assess deprivation effects in 22 male ST users in a randomized crossover study, and observed significant increases in total withdrawal, craving and irritability scores after 24 and 48 hours of abstinence from ST. The authors reported that sensory attributes of ST play an important role in ST withdrawal and craving since a nonnicotine herbal substitute significantly reduced abstinence effects. The findings may have limited generalizability because subjects had low nicotine dependence.

#### **7.5.2-1.6.5.4. Nicotine Dose-Response**

Based on the results of [Hatsukami et al. \(2011\)](#) in 99 cigarette smokers (summarized in [Section 7.5.2-1.6.5.2](#)), higher nicotine content alone in ST products may not provide greater satisfaction. The results suggest that satisfaction may be more related to other product features such as taste. This finding is generally consistent with the results reported in a study by [Blank and Eissenberg \(2010\)](#) in which no differences in craving, withdrawal symptoms/relief were observed between Ariva (lower-nicotine-content tobacco tablet) and Camel snus (higher-nicotine-content tobacco pouch) in 21 cigarette smokers ([Section 7.5.2-1.6.5.2](#)). However, [Kotlyar et al. \(2007\)](#) reported that a product with higher nicotine content (i.e., Copenhagen® ST) was associated with greater exposure to nicotine, the highest scores on several subjective measures (e.g., satisfaction, good effects, strength), and the lowest scores on craving, as compared with those for lower nicotine content ST (Ariva and Stonewall tobacco tablets and Revel ST pouch) and NRT (Commit 4 mg nicotine lozenge) in 10 ST users ([Section 7.5.2-1.6.5.2](#)). In another study, in this case using 28 cigarette smokers, [Cobb et al. \(Cobb et al., 2010\)](#) reported decreases in craving and intention to smoke for Camel snus (higher nicotine content tobacco pouch), but not for Ariva (lower-nicotine-content tobacco tablet) or, for the most part, for Marlboro snus, also a lower-nicotine-content product, suggesting a nicotine dose response. However, QUEST cigarettes, which contain very low levels of nicotine (0.05 mg nicotine), suppressed withdrawal symptoms and reduced cravings in a similar manner to subjects’ own brand cigarettes (1.1 mg nicotine), supporting the importance of sensory attributes of tobacco products in general ([Section 7.5.2-1.6.5.2](#)).



[Coffey and Lombardo \(1998\)](#) reported that participants (n = 24) liked their own ST brand significantly more than all other administrations of ST with differing nicotine content (e.g., 0 percent ST [no nicotine content], 50 percent ST), but reductions in urge to use were similarly decreased across the different nicotine content conditions. A similar finding was reported in smokers in whom liking was highest for the high-nicotine–content condition, but craving was similarly reduced under high- and low-nicotine–content smoking conditions ([Rose, Behm, & Levin, 1993](#)), indicating that the effect is not specific to ST products.

[Table 7.5.2-1-5](#) presents a summary of the identified publications related to the PK ([Section 7.5.2-1.6.5.1](#)) and PD effects ([Section 7.5.2-1.6.5.2](#)) of acute and repeated ST administration, the PD effects of ST withdrawal ([Section 7.5.2-1.6.5.3](#)), and nicotine dose-response ([Section 7.5.2-1.6.5.4](#)).

**Table 7.5.2-1-5: Literature Evaluating the Pharmacokinetics and Pharmacodynamic Effects of ST and Its Withdrawal**

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
Pharmacokinetics and Subjective Effects of ST							
(Cobb et al., 2010)	Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers	Randomized crossover clinical laboratory study  N = 28 smokers (Virginia)	Plasma nicotine concentrations		QSU Brief	Direct Effects of Tobacco/Nicotine	Strengths: Randomized crossover design Acute effects comparison across multiple products in controlled setting  Limitations: Longer exposure/ experience period not assessed
			QSU Brief Direct Effects of Nicotine VAS	Marlboro® snus	No change in withdrawal, ↓ in craving at select time point	↑ pleasant vs. baseline**	
			Direct Effects of Tobacco VAS	Camel® snus	↓ in withdrawal and craving at select time points	↑ pleasant at select time points**	
				Ariva® tobacco tablet	No change in withdrawal or craving	↑ pleasant vs. baseline**	
				Commit® nicotine lozenge	↓ in withdrawal at select time points; ↓ in craving at all time points*	No change	
				Own brand cigarette	↓ in withdrawal and craving vs. baseline and noncombustibles	↑ vs. baseline and noncombustibles	
			*second administration; **first administration. Cigarette associated with highest and earliest peak plasma nicotine concentrations relative to all other products (Camel snus, Marlboro snus, Ariva, Commit, Sham cigarette, Quest cigarette).  Noncombustible tobacco products delivered less nicotine than cigarettes, and did not suppress withdrawal symptoms and cravings as effectively as combustible products. Noncombustible tobacco products (with exception of Commit) were associated with increased positive effects, but less than cigarettes.				

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
(Kotlyar et al., 2007)	Nicotine pharmacokinetics and subjective effects of three potential reduced exposure products, moist snuff and nicotine lozenge	Randomized crossover clinical laboratory study  N = 10 Copenhagen® ST users (Minnesota)	Plasma nicotine concentrations  Withdrawal symptoms, total score and craving  Subjective effects 10-point scale (liking and other drug effects)		Withdrawal and Craving	Subjective Effects	Strengths: Randomized crossover design  Limitations: Use of Copenhagen® as product in study enrolling Copenhagen® users may have confounded results/limited generalizability. Small sample size
				Copenhagen® loose ST	↓ craving and withdrawal symptoms over time; ↓ craving vs. lozenge and other ST products; ↓ in withdrawal symptoms vs. Revel	↑ good effects, satisfaction, liking, desire, strength vs. lozenge and other ST products ↔ negative effects, alert, drowsy, relaxation, jitteriness, energetic vs. lozenge and other ST products	
				Ariva® tobacco tablet	↓ craving and withdrawal symptoms over time; ↓ craving vs. Revel	Not reported	
				Stonewall® tobacco tablet	↓ craving and withdrawal symptoms over time; ↓ craving vs. Revel	Not reported	
				Revel® ST pouch	↓ craving and withdrawal symptoms over time	Not reported	
				Commit® nicotine lozenge	↓ craving and withdrawal symptoms over time; ↓ craving vs. Revel	↑ feeling high vs. Copenhagen® and other ST products	
				Copenhagen® ST associated with highest AUC and C <sub>max</sub> as compared with the AUC and C <sub>max</sub> for all other products; C <sub>max</sub> of Commit higher compared with Ariva, Stonewall, and Revel.  Copenhagen® ST associated with highest nicotine exposure, largest reductions in craving, and highest scores on product effects and liking.  Commit associated with higher nicotine exposure and similar or			

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings				Comments
				superior craving reduction as compared with that for tablets and pouch (lower nicotine).  Lower nicotine content products unlikely to be more effective than NRT in increasing ST quit rates.				
(Fant et al., 1999)	Pharmacokinetics and pharmacodynamics of moist snuff in humans	Randomized crossover clinical laboratory study	Plasma nicotine concentrations		Peak Craving	Peak Strength	Peak Liking	Strengths: Randomized crossover design Acute effects comparison across multiple ST products in controlled setting Within-subject evaluation of exposure and response
			Subjective effects	Copenhagen® loose ST	29.9	85.6	38.0	
		N = 10 male ST users (Maryland)	VAS including product strength, liking, craving	Skoal® Long Cut Cherry loose ST	20.9	51.2	63.9	
				Skoal® Original Wintergreen loose ST	20.7	62.4	49.4	
				Skoal® Bandits pouch ST	20.2	23.7	34.2	
				C <sub>max</sub> and AUC: Copenhagen® > Skoal Cherry ≈ Skoal Wintergreen > Skoal Bandits  T <sub>max</sub> : ~ 5-10 minutes after removal of product  Nicotine absorption was variable across subjects despite same amount of ST administered.  Subjective effects followed time-course similar to plasma nicotine levels over first 15 minutes and then leveled off, possibly as a function of tolerance development.  Product strength varied as a function of nicotine content (Copenhagen® >> Skoal Bandits); however, peak liking and craving were not dose-dependent.				Limitations: Overall response to product not assessed ST brand of choice may have confounded responses Small sample size

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Benowitz, 1997)	Systemic absorption and effects of nicotine from smokeless tobacco	Review of clinical laboratory studies	Nicotine concentrations	Significant variation across subjects in amount of nicotine absorbed from same-sized dose of ST.  Blood nicotine concentrations similar in smokers and ST users during <i>ad libitum</i> use.	<i>Strengths:</i> Review of multiple studies
(Gritz et al., 1981)	Plasma nicotine and cotinine concentrations in habitual smokeless tobacco users	Single-arm clinical laboratory study  N = 12 male ST users (college students) (California)	Plasma nicotine and cotinine concentrations  Subjective effects	Plasma nicotine: mean peak of 21.6 ng/mL after 6-8 hour <i>ad libitum</i> chewing  Plasma nicotine and cotinine concentrations did not correlate with tobacco consumption on test day or with self-reported consumption.  Little effect reported by subjects on physiologic and stimulation scales (ranging between "not at all" and "a little"); slightly higher for relaxation/satisfaction ("somewhat").  No correlation between self-reported use and actual use, indicating lack of precision in recalling daily intake.  Large changes in plasma nicotine/cotinine associated with decrease in relaxation/satisfaction (Pearson’s $r = -0.60/-0.55$ , $p < 0.05$ ) and increase in stimulation ( $r = 0.71$ , $p < 0.01$ , cotinine only).  Nicotine and cotinine concentrations in most subjects similar to those of cigarette smokers.	<i>Strengths:</i> <i>Ad libitum</i> consumption, increasing face validity  <i>Limitations:</i> Single arm study No direct comparison to smokers Infrequent sampling and time since last use not controlled relative to sampling period. Analysis did not control for swallowing tobacco juice. Small sample size Self-report – recall bias

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
Actual Use							
(D. Hatsukami et al., 2011)	Oral tobacco products: Preference and effects among smokers	Partially-blinded clinical laboratory study	Sampling period: Product sampling behavior		Sampling period: Relief from Withdrawal/Urges (% subjects)	Cessation period: Satisfaction/ Craving relief/ Withdrawal relief (6-pt Likert)	Strengths: Multiple product comparison in moderate sample size
				Camel snus (1.74–1.97 mg nicotine)	28.87%/28.57%	4.7/3.9/4.3	Randomized product exposure
		N = 99 treatment-seeking smokers entered sampling period; 97 entered 2-week cessation period	Product perception, including relief from withdrawal, craving, ease of use, general satisfaction and likeability	Stonewall lozenge (0.28-0.57 mg)	26.8%/21.43%	4.3/4.0/4.5	Subjects permitted to use product <i>ad libitum</i> ("real-world") Subjects blinded to brand of snus
				Ariva tobacco tablet (~0.25 mg)	19.59%/18.37%	3.8/3.1/3.5	
				Marlboro snus (0.14-0.38 mg)	17.53%/19.39%	4.2/3.2/3.8	
				General snus (3.37 mg)	7.22%/12.24%	---	
				No difference in amount used across products during sampling period or during cessation period.			
		Number of cigarettes	Proportion (~ 25%) of subjects choosing Ariva, Camel, Marlboro snus, and Stonewall lozenge for cessation period similar; no subject chose General snus for the cessation period.			Limitations: Short sampling period may have limited subjects' experience with each product Reported use of ST after study may be confounded with availability Multiple comparisons unadjusted; therefore, statistical significance of results should be interpreted with caution	
			Product use decreased over time during cessation period for all products, with Ariva product use significantly less than Stonewall and Camel snus; cigarette use increased over time and was higher for those who chose Marlboro snus vs. Stonewall or Camel snus.				
			Products with higher levels of nicotine were rated more highly on measures such as satisfaction, craving relief and withdrawal relief.				
			Abstinence rates significantly higher for Camel snus vs. Ariva, Stonewall, and approaching significance for Marlboro snus; subjects more likely to continue using Camel snus during follow-up period.				

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(D. Hatsukami et al., 2013)	Subjective responses to oral tobacco products: Scale validation	Partially- blinded clinical laboratory study  N = 99 treatment- seeking smokers entered sampling period; 97 entered 2-week cessation period (Minnesota, Oregon)	Product perception, including relief from withdrawal, craving, ease of use, general satisfaction and likeability	<p>General snus rated significantly lower than all other products on satisfaction, psychological reward, aversion, relief, ease of use, comfort of use, and concern for dependence.</p> <p>Subjective responses during the sampling period significantly correlated with product choice for the cessation period, including satisfaction and relief, and negatively correlated with aversion. Higher nicotine content associated with greater psychological reward and concern for dependence (Camel snus and Stonewall).</p> <p>Satisfaction reported during the sampling period significantly predicted product intake during the cessation period.</p> <p>Results consistent with Hatsukami et al. 2011 findings, with subjective responses significantly lower for General snus.</p> <p>Validity of the scale used supported by the relationship between subjective responses and product choice (i.e., higher ratings on craving and withdrawal relief and satisfaction associated with choosing a particular product).</p>	<p><i>Strengths:</i>  Multiple product comparison in moderate sample size  Randomized product exposure  Subjects permitted to use product <i>ad libitum</i> ("real-world")  Subjects blinded to brand of snus</p> <p><i>Limitations:</i>  Short sampling period may have limited subjects' experience with each product  Reported use of ST after study may be confounded with availability  Multiple comparisons unadjusted; therefore, statistical significance of results should be interpreted with caution.</p>

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Blank & Eissenberg, 2010)	Evaluating oral noncombustible potential-reduced exposure products for smokers	Randomized crossover clinical study  N = 21 cigarette smokers (Virginia)	Product use  Urine cotinine concentrations  Hughes-Hatsukami questionnaire  QSU  Direct effects of nicotine	Product use: Own cigarettes > Ariva and Camel snus.  Cotinine concentrations: cigarettes > Ariva and Camel snus.  Mean craving scores increased over 5-day period for Ariva and Camel snus conditions, but not for cigarettes; scores for Ariva and Camel snus significantly higher than that for cigarettes.  QSU Irritability/frustration/anger significantly lower for cigarettes.  Direct effects of nicotine scores significantly higher for cigarettes than those for. Ariva and Camel snus.  Ratings of "Dislike" significantly higher for Ariva and Camel snus than those for cigarettes.  Ariva and Camel snus did not fully suppress tobacco abstinence symptoms, delivered less nicotine, and were less enjoyable than cigarettes; therefore, Ariva and Camel snus was unlikely to substitute for cigarettes in smokers.	<i>Strengths:</i> Randomized crossover design Actual use patterns captured in natural <i>ad libitum</i> environment  <i>Limitations:</i> High attrition, mostly related to lack of compliance during noncigarette conditions Did not assess compliance during outpatient periods
<b>Subjective effects of ST Withdrawal</b>					
(Dennis E. McChargue et al., 2002)	Effect of non-nicotinic moist snuff replacement and lobeline on withdrawal symptoms during 48-h smokeless tobacco deprivation	Randomized crossover clinical laboratory study  N = 22 male ST users (Oklahoma)	Minnesota Nicotine Withdrawal Scale	Total withdrawal, craving, and irritability scores increased following abstinence period of 24 and 48 hours compared with baseline scores.  BACCOFF (herbal product) administration mimicked sensory features of ST use and decreased severity of withdrawal symptoms.  Sensory attributes of nonnicotinic substitute can significantly reduce withdrawal severity over 48-hour abstinence period.	<i>Strengths:</i> Randomized crossover design  <i>Limitations:</i> Subjects reported low dependence; results may not reflect more dependent users Did not verify abstinence biochemically



Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(D. E. McChargue & Collins, 1998)	Differentiating withdrawal patterns between smokers and smokeless tobacco users	Parallel-group clinical laboratory study  N = 10 ST users  N = 9 cigarette smokers (Oklahoma)	Withdrawal symptom checklist	Withdrawal and craving scores increased during the 48-hour deprivation condition compared with continued use condition; however, no differences between ST users and cigarette smokers.  Downward trend in craving and withdrawal scores in nondeprivation condition over 48 hours underscores importance of stabilization period under nondeprivation condition and that reliance on one baseline measure may not accurately reflect withdrawal severity.	<i>Strengths:</i> Direct comparison between ST users and cigarette smokers 48 hour assessment period allowed comparison of effects under more stabilized conditions.  <i>Limitations:</i> Small sample size Withdrawal severity lower in this study than in other published literature Difference in extent of nicotine exposure between the 2 groups may influence withdrawal
(D. Hatsukami et al., 1992)	Smokeless tobacco abstinence effects and nicotine gum dose	Randomized parallel group clinical laboratory study  Study 1: N = 20 male Copenhagen® ST users  Study 2 (double-blind): N = 60 male Copenhagen® ST users (Minnesota)	Saliva cotinine concentrations  POMS  Stanford Sleep Scale  Withdrawal symptom checklist (self-rated and observer-rated)  Reaction time task	Study 1 (Group 1, continued <i>ad libitum</i> ST use; Group 2, 5-day abstinence): ST abstinence (Group 2) associated with increased craving, difficulty concentrating, restlessness, hunger, increased eating and total withdrawal score; increased awakenings; and increased reaction time. Continued ST use (Group 1) associated with decreases in symptoms.  Study 2: (5-day ST abstinence with <i>ad libitum</i> nicotine gum 0 mg (Group 1), 2 mg (Group 2) or 4 mg (Group 3) During ST abstinence, use of nicotine-containing gum increased cotinine levels in a dose-dependent manner (0 mg < 2 mg < 4 mg); however, no group differences seen in severity of withdrawal symptoms, including craving, difficulty concentrating, restlessness, hunger, increased eating, total withdrawal score; and increased reaction time. In subjects with high baseline cotinine levels (sub-analysis), nicotine gum decreased cravings.  Total withdrawal scores lower in ST users compared with previous	<i>Strengths:</i> Randomized, controlled study (1 and 2) Study 2, double-blind design  <i>Limitations:</i> Inability to fully verify potential ST use during abstinence period Small sample size Study 1, open-label design; knowledge of group assignment, particularly abstinence group, may have over-inflated responses

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
				<p>reports in cigarette smokers, and fewer number of withdrawal symptoms experienced. No anxiety or irritability reported in abstinent ST users, unlike cigarette smokers.</p> <p>Lack of nicotine gum dose response on withdrawal symptom suppression may be related to strong placebo effect of nicotine gum or milder withdrawal symptomatology (compared with cigarette smokers).</p>	
(D. Hatsukami et al., 1987)	Physiologic and subjective changes from smokeless tobacco withdrawal	<p>Clinical laboratory study</p> <p>N = 16 Copenhagen® ST users</p> <p>N = 11 cigarette smokers (Minnesota)</p>	<p>POMS</p> <p>Stanford Sleep Scale</p> <p>Craving VAS</p> <p>Withdrawal symptom checklist (self-rated and observer-rated)</p> <p>Saliva cotinine levels</p> <p>Amount used</p>	<p>Increased craving and POMS-confusion, number of awakenings, and total score withdrawal symptom checklist for both ST users and cigarette smokers during abstinence (<math>p &lt; 0.05</math>); however, only cigarette smokers experienced increased anger/hostility and tension/anxiety and a decrease in vigor (<math>p &lt; 0.05</math>), and effects on other measures were generally greater than those for ST users.</p> <p>No difference in baseline cotinine levels between ST user and smokers.</p> <p>Craving significantly associated with baseline cotinine levels (Pearson’s <math>r = 0.67</math>), duration (<math>r = 0.44</math>) and number of dips (<math>r = 0.49</math>) per day in ST users (<math>p &lt; 0.05</math>).</p> <p>Cotinine levels significantly associated with self-reported total withdrawal symptoms (<math>r = 0.49</math>), and between amount of ST per day and observer-rated total withdrawal symptoms (<math>r = 0.54</math>; <math>p &lt; 0.05</math>).</p> <p>Withdrawal symptoms similar in Copenhagen® ST users as compared with those for cigarette smokers; however, severity of symptoms was less, despite similar levels of nicotine intake.</p> <p>Topography of ST use may be better predictor of nicotine intake vs. amount used.</p>	<p><i>Strengths:</i></p> <p>Direct comparison of withdrawal symptomatology between ST users and cigarette smokers</p> <p><i>Limitations:</i></p> <p>Different period of abstinence between ST users (3 days) and smokers (5 days [only first 3 days analyzed]), with potential greater anticipation of withdrawal in smokers, although authors' argue that symptoms in cigarette smokers similar to those reported after 24 to 72 hours of abstinence</p> <p>Self-report – recall bias</p>

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
<b>ST Dose-Response</b>					
(Coffey & Lombardo, 1998)	Effects of smokeless tobacco-related sensory and behavioral cues on urge, affect, and stress	Randomized crossover clinical laboratory study  N = 24 male ST users (Mississippi)	Urge for ST VAS	Urge for ST decreased for all ST conditions, independent of nicotine content (i.e., no ST > 0%, 50%, 100% ST, $p < 0.05$ , where % refers to nicotine-containing ST content of product administered).  ST sensory and behavioral cues (e.g., handling tin, placing a dip in the mouth, smell, taste, mild burning sensation) decreased urge for ST that was independent of nicotine content.	<i>Strengths:</i> Randomized crossover design Acute effects comparison across ST product with varying nicotine content  <i>Limitations:</i> Absence of control for general oral stimulation Limited sampling time

#### 7.5.2-1.6.6. Dependence on ST

The literature search yielded 17 studies evaluating dependence on ST. Sixteen of these studies were cross-sectional, and one was longitudinal in design. Most studies (n = 12) included adults, and five studies evaluated dependence in adolescents (one of which included young adults). Seven of the studies included treatment-seeking adult ST users. Although the ability to directly compare levels of tobacco dependence between smokers and ST users is limited as there are no measures of dependence validated across tobacco products, a few studies enabled a direct comparison of dependence in ST users with cigarette smokers (6 studies) or NRT users (1 study). Six studies included measurement of nicotine/cotinine levels as an objective marker of tobacco use, as previous studies with smokers have shown that nicotine/cotinine concentrations are a significant predictor of cigarette dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991; C. S. Pomerleau, Pomerleau, Majchrzak, Kloska, & Malakuti, 1990). Measures of dependence commonly included in these studies were TTFU, FTND or Fagerström Tolerance Questionnaire (FTQ) (including specific items and modified forms), and subjective withdrawal symptoms, including craving and difficulty abstaining.

Five studies evaluated dependence in adolescent ST users. In a large, nationally representative survey of adolescent and young adults, the Centers for Disease Control (Centers for Disease Control and Prevention, 1994) reported that withdrawal symptoms and correlates (e.g., lifetime use, frequency of use) were similar between smokers (n = 2,121) and ST users (n = 470), but in less frequent users (1-14 days out of the past 30 days), withdrawal symptoms may be less in ST users than in smokers. Apelberg et al. (Apelberg et al., 2014) reported that adolescent ST users (n = 198) exhibit some symptoms of dependence at levels similar to cigarette smokers, including craving and desire to use in the past 30 days, and wanting to use ST within 30 minutes of waking; however, there was a trend for reduced feelings of irritability and restlessness as compared with that for smokers. DiFranza et al. (Joseph R. DiFranza, Sweet, Savageau, & Ursprung, 2012) assessed tobacco dependence in adolescent smokers (n = 139) and ST users (n = 85) reporting more than 100 lifetime uses, and reported that dependence was similar between smokers and ST users, as measured by the Hooked on Nicotine Checklist, Autonomy over Smoking Scale, latency to withdrawal and pleasure derived from tobacco use; however, the study did not differentiate dual use from exclusive use and data were collected in a small geographical location, limiting generalizability. Riley et al. (Riley et al., 1989; Riley, Barenie, Woodard, & Mabe, 1996) reported that in ST ever triers (n = 740 and n = 3,726, respectively), approximately 9%-13% reported difficulty quitting and approximately 8%-10% reported feeling addicted to ST. Use for over 1 year associated with a 12-fold higher likelihood of reporting being addicted relative to use for less than 1 year. Thus, despite limited lifetime use, adolescents endorse symptoms of nicotine dependence similar in type and magnitude to same-aged smokers (with the possible exception of irritability and restlessness) and their perceived addiction increases with amount and frequency of use.

Five studies examined ST dependence in current adult users, three of which included a comparison with smokers. Rodu and Cole (2010) conducted a large nationally representative survey of TTFU in daily smokers (n = 10,478) and ST users (n = 1,176), as this is a common

measure of dependence. A similar proportion of light smokers (10%) and ST users (9%) reported use within 5 minutes of waking, which was notably lower than that for moderate smokers (22%) and heavy smokers (47%). However, relative to light smokers, ST users (any level of use) were less likely to use within 30 minutes of waking (adjusted OR = 0.74, 95% CI: 0.62-0.89), whereas moderate and heavy smokers were more likely to use within 30 minutes of waking (adjusted OR = 3.88; 95% CI: 3.51-4.28; and 12.28; 95% CI: 10.57-14.27, respectively). [Kram et al. \(2014\)](#) found that the proportion of participants reporting minimal, moderate, and high nicotine dependence (based on FTND) was similar between exclusive smokers (n = 483) and exclusive ST users (n = 241) in the military; however, no formal analyses were conducted between these two groups because the study was focused on dual users. [Hatsukami et al. \(1999\)](#) reported that, among 402 treatment-seeking ST users, the majority reported TTFU within 30 minutes of waking (60%) and swallowing tobacco juice (74%), and approximately half reported use when ill, difficulty in refraining from use when prohibited, and the morning chew being the most difficult to give up. In a smaller study of native Alaskans ([Renner et al., 2013](#)), a notably smaller proportion of ST users (11.8%) reported TTFU within 30 minutes of waking than was reported by smokers (44.2%). In a scale validation study involving 100 ST users, [Mushtaq et al. \(2014\)](#) reported a significant correlation between salivary cotinine and dependence scores ( $r = 0.267$ , Cronbach’s  $\alpha = 0.925$ ), with subscales of loss of control and craving, and tolerance and automaticity (which includes TTFU < 30 min) correlating positively with cotinine levels as well. Unlike dependence in smokers, however, Mushtaq et al. found that social and environmental motives and sensory processes do not appear to play as large a role in ST dependence.

[Thomas et al. \(2006\)](#) measured nicotine dependence and baseline cotinine levels in a longitudinal study of 68 treatment-seeking ST users, and reported that dependence scores (measured using the Fagerström Tolerance Questionnaire Modified for ST users, FTQ-ST) were modestly positively correlated with nicotine and cotinine concentrations as well as amount of tobacco used ( $r = 0.32$ - $0.41$ ). A higher FTQ-ST score was associated with a significantly reduced likelihood of abstinence at 3 months after quitting, but no association was observed at the 6-month time point. Three additional studies evaluated dependence in ST users (various measures, including modified FTQ, FTND-ST) in relation to cotinine levels ([R. G. Boyle, Jensen, Hatsukami, & Severson, 1995](#); [Jon O. Ebbert, Patten, & Schroeder, 2006](#); [Ferketich, Wee, Shultz, & Wewers, 2007](#)); n = 42–256 subjects). Although significant correlations were observed, these were modest, the amount of variance in cotinine explained by the scales was limited, and the scales were reported to have low internal consistency. Overall, the literature findings indicate that, in contrast with that for smokers, the relationship between nicotine/cotinine levels resulting from ST use and dependence/use is modest and may in part be related to swallowing tobacco juice.

[Oliver et al. \(2013\)](#) examined level of dependence in 468 adult users of flavored and nonflavored ST from five studies, as there have been reports that flavored products might be more addictive. While users were more likely to switch from nonflavored to flavored products rather than the other way around, flavored ST users did not have higher nicotine dependence than nonflavored ST users. In fact, flavored ST users generally had lower cotinine levels and used less ST per day and were less likely to report TTFU within 30

minutes of waking (74.7 percent nonflavored ST users vs. 63.5 percent flavored ST users,  $p < 0.05$ ).

In a reanalysis of multiple tobacco cessation studies, Fagerström and Eissenberg ([K. Fagerstrom & Eissenberg, 2012](#)) reported on the success rate of participants randomized to the placebo arm of the trial as a proxy measure of difficulty in abstaining from tobacco use. Approximately 25% (range: 19.1%-33.0%) of ST users remained abstinent at the follow-up (6 months to 1 year, depending on the study), whereas approximately 10% (range: 9.8%-11.2%) of smokers remained abstinent at the time of follow-up; abstinence from NRT was highest at 36% (from one trial). Taking the results together, the authors concluded that dependence was highest among smokers, lowest in NRT users, and intermediate for ST users.

[Table 7.5.2-1-6](#) summarizes the key results of each identified study related to the evaluation of dependence on ST.

**Table 7.5.2-1-6: Literature Evaluating Smokeless Tobacco Dependence**

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
<b>Adolescents</b>					
(Apelberg et al., 2014)	Symptoms of tobacco dependence among middle and high school tobacco users: Results from the 2012 National Youth Tobacco Survey	Cross-sectional. National school-based survey  N = 3,454 middle and high school tobacco users (U.S.)	Self-reported symptoms of tobacco dependence	<p>Polytobacco users = 62.4%</p> <p>Exclusive users: Cigarettes: 45.0% ST = 17.1%</p> <p><i>ST users</i> Strong tobacco cravings in past 30 days: AOR (95% CI) = 0.9 (0.6-1.5) (reference = cigarette users)</p> <p>Strong desire to want to use tobacco in past 30 days: AOR (95% CI) = 1.0 (0.5-2.1) (reference = cigarette users)</p> <p>Feeling irritable/restless when not using tobacco for a while: AOR (95% CI) = 0.6 (0.4-1.0) (reference = cigarette users)</p> <p>Wanting to use tobacco within 30 minutes of waking: AOR (95% CI) = 0.6 (0.2-1.5) (reference = cigarette users)</p> <p>Adolescent ST users exhibit some symptoms of dependence at levels similar to exclusive cigarette smokers.</p> <p>A trend for reduced feelings or irritability and restlessness during abstinence reported for ST vs. cigarette smokers.</p>	<p><i>Strengths:</i> Nationally representative Large sample size Multivariate logistic regression</p> <p><i>Limitations:</i> Cross-sectional design, therefore cannot evaluate onset of tobacco dependence symptoms relative to age at initiation Limited number of dependence measures assessed Did not differentiate between exclusive ST and cigarette users in most analyses Self-report - recall bias</p>

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings		Comments
(Joseph R. DiFranza et al., 2012)	The assessment of tobacco dependence in young users of smokeless tobacco	Cross-sectional. Survey  N = 139 adolescent smokers  N = 85 adolescent ST users (> 100 lifetime uses) (Florida)	Mean (SD)	ST users	Smokers	Strengths: Direct comparison between smokers and ST users
			HONC (10 items)	5.42 (3.22)	5.31 (3.32)	
			AUTOS (12 items; score range of 0-36)	16.7 (8.78)	16.1 (10.0)	Limitations: Cross-sectional Small sample size, particularly ST users Did not exclude dual users Limited geographic representation Rudimentary categorization of history of use
			Latency to Withdrawal (hr)	166 (219)	147 (202)	
			Pleasure from tobacco use (10-point scale)	6.83 (1.61)	6.61 (2.38)	
				No difference in level of dependence between smokers and ST users		
(Riley et al., 1996)	Perceived smokeless tobacco addiction among adolescents	Cross-sectional. Survey  N = 3,726 adolescent ST ever triers (nonurban southeastern U.S.)	Difficulty quitting  Addicted to ST	Difficulty quitting ST: 13% Addicted to ST: 10%  Use of ST >1 year associated with higher likelihood of reporting being addicted than in those using ST <1 year (OR = 12.65, 95% CI = 10.94-14.66).  Perceived addiction increased with years of use, frequency of use per day, and hours of use per day.  Difficulty quitting increased with increasing ST use.		Strengths: Large sample size  Limitations: Cross-sectional survey Self-report - recall bias Limited geographic representation
(Centers for Disease Control and Prevention, 1994)	Reasons for tobacco use and symptoms of nicotine withdrawal among adolescent and young adult tobacco users--United States, 1993	Cross-sectional. National telephone survey of adolescents and young adults  N = 2,121 smokers  N = 1,925 former smokers	Use because of difficulty quitting  Use because of relaxation  Withdrawal symptoms: urge to use, irritability,	Use because of difficulty quitting increased with lifetime use, frequency of use, and intensity of use of ST and cigarettes.  Use for relaxation more likely reported by smokers vs. ST users.  Withdrawal symptoms increased with frequency and intensity of use similarly in smokers and ST		Strengths: Nationally representative Large sample size  Limitations: Cross-sectional design, therefore cannot evaluate trajectory of tobacco dependence within individual



Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
		N = 470 ST users  N = 1,216 former ST users (U.S.)	difficulty concentrating, feeling hungry, sad when quit/tried to quit	users.  Among those who used tobacco on 1-14 of past 30 days, smokers more likely to report symptoms of withdrawal vs. ST users.  Withdrawal symptoms and correlates generally similar between smokers and ST users, although in less frequent users, withdrawal symptoms may be less in ST users vs. smokers.	Limited number of dependence measures assessed
(Riley et al., 1989)	Typology and correlates of smokeless tobacco use	Cross-sectional. Survey  N = 740 adolescent ST ever triers (nonurban southeastern U.S.)	Difficulty quitting  Addicted to ST	Difficulty quitting: 8.7% Addicted to ST: 8.4%  Increased use (hours per day) associated with being addicted to ST.	<i>Strengths:</i> Moderate sample size  <i>Limitations:</i> Cross-sectional survey Self-report - recall bias Limited geographic representation
<b>Adults</b>					
(Kram et al., 2014)	Dual tobacco user subtypes in the U.S. Air Force: Dependence, attitudes, and other correlates of use	Cross-sectional. Survey  N = 8,956 U.S. Air Force recruits (N = 483 exclusive smokers; N = 241 exclusive ST users) (U.S.)	FTND score (points) (mild = < 4; moderate = 4-6; highly = 7-10)	Proportion of minimal, moderate, and highly nicotine dependent similar between exclusive smokers (54.8%/37.8%/7.4%) and exclusive ST users (56.6%/34.4%/9.0%).  Level of dependence similar between exclusive smokers and ST users.	<i>Strengths:</i> Large sample size  <i>Limitations:</i> Limited generalizability to general population Self-report - recall bias Analysis did not consider comparisons between exclusive smokers and ST users

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Mushtaq et al., 2014)	A multiple motive/multi-dimensional approach to measure smokeless tobacco dependence	Development of ST dependence scale  N = 100 male ST users (Oklahoma)	Salivary cotinine  Oklahoma Scale for Smokeless Tobacco Dependence	Correlation between OSSTD score and salivary cotinine, $r = 0.267$ ( $p = 0.009$ ), with Cronbach's $\alpha = 0.925$ .  OSSTD subscales loss of control and craving, tolerance and automaticity, and affiliative attachment positively correlated with cotinine.  OSSTD score significantly correlated with frequency, quantity and duration of use.  OSSTD identified seven latent constructs, which include 23 items to measure ST dependence.  OSSTD has better psychometric properties than FTND-ST.  OSSTD measures ST dependence as a multidimensional construct.	<i>Strengths:</i> Scale included multiple dimensions of ST use Biomarker of tobacco use included Comparison of new scale to previously validated scales  <i>Limitations:</i> Small sample size did not allow for multivariate analysis, and factor analysis not sufficiently powered
(Brad. Rodu, Plurphanswat, & Fagerstrom, 2014)	Time to first use among daily smokers and smokeless tobacco users	Cross-sectional. Survey  N = 10,478 smokers  N = 1,176 ST users (U.S.)	TTFU	AOR (95% CI) for TTFU within 5 min (reference = light smoker) ST user: 1.28 (0.97, 1.68) Moderate smoker: 3.09 (2.65, 3.60) Heavy smoker: 9.09 (7.72, 10.71)  AOR (95% CI) for TTFU within 30 min (reference = light smoker) ST user: 0.74 (0.62, 0.89) Moderate smoker: 3.88 (3.51, 4.28) Heavy smoker: 12.28 (10.57, 14.27)  Dependence among ST users more similar to that of light smokers, with 9% of ST users reporting TTFU within 5 min vs. 10% for light smokers.	<i>Strengths:</i> Nationally representative Large sample size Multivariate logistic regression model  <i>Limitations:</i> Cross-sectional Self-report - recall bias Did not differentiate amount of use in ST group
(Renner et al.,	Tobacco use among	Cross-sectional.		<i>ST users</i>	<i>Smokers</i>
					<i>Limitations:</i>

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings		Comments
2013)	Southwestern Alaska Native people	Survey  N = 76 ST users  N = 163 smokers (Alaska)	TTFU (≥ 30 min)	11.8%	44.2%	Limited generalizability to general population Self-report - recall bias Cross-sectional
				Higher proportion of smokers report TTFU within 30 minutes of waking vs. ST users.		
(Oliver et al., 2013)	Flavored and nonflavored smokeless tobacco products: Rate, pattern of use, and effects	Post hoc analysis of 5 completed treatment or switching studies  N = 468 adult ST users  (Location of studies not reported)	Choice of brand flavor from initiation to regular use	~60% reported mint-flavored product as first product used; ~60% reported current use flavored products, majority using wintergreen flavor.  ST users who first started using nonflavored product more likely to switch to flavored product (vs. other way around); ST users who initiated with mint-flavored product more likely to currently use mint-flavored product.  Flavored ST users had lower cotinine levels, used less ST dips per day, and did not have higher nicotine dependence vs. nonflavored ST users.  Flavored products may not be more addictive, but may facilitate initiation and maintenance of use.		Limitations: Nonrepresentative sample of intervention-seeking ST users Post hoc analysis
Treatment-seeking Adults						
(K. Fagerstrom & Eissenberg, 2012)	Dependence on tobacco and nicotine products: A case for product-specific assessment	Reanalysis of tobacco cessation trials (placebo groups)  (Location of studies not reported)	Success rate in placebo group as proxy of difficulty abstaining	Smokers: 10% (range: 9.8%-11.2%) ST users: 25% (range: 19.1%-33.0%) NRT (gum): 36%  Difficulty quitting cigarettes greater than quitting ST.  Dependence differs across tobacco/nicotine products, with dependence on NRT lowest, leading to more successful cessation, and dependence on cigarettes highest; ST in between. Authors posit a continuum of dependence across various tobacco		Strengths: Review of multiple controlled intervention trials  Limitations: Follow-up periods varied (e.g., 6 months for most ST trials vs. 1 year for NRT trial)

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
				products.  Recommend use of product-specific instruments to assess dependence.	
(Ferketich et al., 2007)	A measure of nicotine dependence for smokeless tobacco users	Cross-sectional. Scale validation study  N = 256 treatment-seeking male ST users (Ohio)	Baseline salivary cotinine  Baseline mFTND score	Cotinine and total score correlation (r) = 0.34  Low internal consistency (Cronbach alpha coefficient = 0.40)	<i>Limitations:</i> Limited geographic representation (Appalachia) Limited number of items used in the scale
(Jon O. Ebbert et al., 2006)	The Fagerström Test for Nicotine Dependence-Smokeless Tobacco (FTND-ST)	Cross-sectional. Scale validation study  N = 42 treatment-seeking ST users (Minnesota)	Baseline serum cotinine  Baseline FTND-ST score  Baseline mFTQ	Correlations (r): FTND-ST Cotinine and total score = 0.53 (p < 0.001) Cotinine and swallow tobacco juice = 0.44 (p = 0.003) Cotinine and morning chew most important = 0.48 (p = 0.001)  (m)FTQ Cotinine and use within 30 minutes of waking = 0.39 (p = 0.01) Cotinine and swallow tobacco juice = 0.41 (p = 0.008)  Strongest correlation between cotinine levels and use within 30 minutes of waking.	<i>Limitations:</i> Small sample size of heavy ST users limiting generalizability and power

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
				Low internal consistency for both scales (Cronbach's alpha = 0.47), similar to that for scales assessing cigarette dependence.	

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Thomas et al., 2006)	Measuring nicotine dependence among smokeless tobacco users	Validity assessment of nicotine dependence scales  N = 68 treatment-seeking adult ST users (Minnesota)	Baseline cotinine  Baseline FTQ-ST  Baseline DIS-IV-ND  Abstinence at 3 and 6 months	FTQ-ST score positively correlated with amount of tobacco used (e.g., tins/week, $r = 0.41$ ) and nicotine/cotinine concentrations ( $r = 0.32$ and $0.40$ ).  Agreement between FTQ-ST and DIS-IV not higher than chance.  Higher FTQ-ST score associated with reduced likelihood of tobacco abstinence at 3 months (OR = 0.76, 95% CI: 0.61-0.96).  Neither FTQ-ST nor DIS-IV predicted tobacco abstinence at 6 months.  FTQ-ST correlated with cotinine, amount of tobacco use and reduced likelihood of abstinence at 3 months. Poor concordance between FTQ-ST and DIS-IV, indicating these are measuring different constructs of nicotine dependence.	<i>Limitations:</i> Small sample size limiting statistical power and generalizability
(Jon O. Ebbert et al., 2005)	A survey of characteristics of smokeless tobacco users in a treatment program	Cross-sectional. Survey  N = 60 current ST users who underwent treatment (Minnesota)	TTFU ( $\leq 30$ min)  Difficulty abstaining  Use despite illness  Craving after 2 hours without ST	TTFU ( $\leq 30$ min): 48%  Difficulty abstaining: 35%  Use despite illness: 32%  Craving after 2 hours without ST: 55%  Continuing ST users had high levels of nicotine dependence, lack of motivation, withdrawal symptoms and stress.	<i>Limitations:</i> Cross-sectional Small sample size; limited generalizability Did not report baseline measures (at time of treatment); therefore, could not evaluate change over time

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(D. Hatsukami et al., 1999)	Characteristics of smokeless tobacco users seeking treatment	Cross-sectional. Survey  N = 402 treatment-seeking ST users (Minnesota)	Baseline salivary cotinine  Baseline mFTQ, including:  Morning chew most difficult to give up  Difficulty refraining from use in places prohibiting use  Use when ill  Swallow tobacco juice  TTFU ( $\leq 30$ min)	Baseline salivary cotinine mean (SD): 489.6 ng/mL (296.6)  Baseline mFTQ: Morning chew most difficult to give up: 46.4% Difficulty refraining from use in places prohibiting use: 47.3% Use when ill: 50.3% Swallow tobacco juice: 74% TTFU ( $\leq 30$ min): 60%  Treatment-seeking ST users show high levels of dependence and nicotine exposure.	<i>Strengths:</i> Moderate sample size  <i>Limitations:</i> Cross-sectional survey Self-report - recall bias No correlation to evaluate dependence measures with cotinine Limited generalizability
(R. G. Boyle et al., 1995)	Measuring dependence in smokeless tobacco users	Cross-sectional. Scale validation study  N = 221 treatment-seeking ST users	Baseline salivary cotinine level  Tobacco dependence (2 versions of mFTQ)	Correlation between cotinine and mFTQ score (2 versions): Version 1: 0.47 ( $p < 0.001$ ); chew within 30 minutes of waking and keeping dip in mouth all the time significantly correlated with cotinine ( $r = 0.43, 0.36$ , respectively).  Version 2: 0.33 ( $p < 0.01$ ); time to first chew significantly correlated with cotinine ( $r = 0.30$ ).  Multiple regression: Version 1: Use of ST within 30 minutes of waking, strong cravings if abstinence $> 2$ hours and length of time chew in mouth contributed significantly to prediction of cotinine level.  Version 2: Number of tins/week, frequency of	<i>Limitations:</i> Cotinine limited as measure of nicotine exposure in ST users Overestimation of cotinine in ST users who swallow tobacco juice

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
				<p>swallowing tobacco juice and time from waking to use chew contributed significantly to prediction of cotinine level.</p> <p>Baseline salivary cotinine correlated with the (m)FTQ, but amount of variance in cotinine explained by the scales was limited (11%-22%), but correlations similar to FTQ and cotinine seen with smokers.</p> <p>Internal consistency low for each scale (Cronbach's alpha: 0.30 and 0.52).</p> <p>Questions specific to use of ST may provide more useful scale of ST dependence.</p>	



#### **7.5.2-1.6.7. Cessation of ST**

The literature search yielded 23 relevant publications related to cessation of ST, including two cross-sectional surveys, 20 clinical trials evaluating various cessation methods, including behavioral interventions, pharmacotherapies, NRT, tobacco-free snuff, and combination therapy (e.g., gum plus behavioral), and one review of pharmacotherapy cessation trials. Most trials were randomized and controlled, although a few were single-arm observational trials. Biochemically confirmed abstinence rates (typically 7-day point prevalence; primary endpoint) were commonly evaluated at 3 and 6 months and in some cases, up to 12 or 18 months. Two trials evaluated tobacco reduction as a primary endpoint rather than abstinence.

##### **7.5.2-1.6.7.1. Relative Cessation Rates Among Tobacco Users**

Fagerström and Eissenberg (2012) have drawn comparisons between cigarettes, ST, and NRT with regard to “difficulty quitting.” In their systematic review of a series of cessation studies, the authors identified an approximately twofold higher rate of cessation (minimum 6-month follow-up, based on Cochrane system criteria) in ST users than in cigarette smokers who were assigned to the placebo group (a proxy measure of difficulty abstaining) in a clinical trial of a NRT or pharmaceutical product. Cessation rates of these placebo groups ranged from 9.8% to 11.2% in smokers and from 19.1% to 33% in ST users. Based on a single trial in long-term NRT users who were previously heavy dependent smokers, the cessation rate of NRT was highest at 36%. This evaluation suggests that cessation of ST is greater than that of cigarettes in the absence of true intervention (i.e., placebo). Indeed, the literature suggests that overall abstinence rates are higher in ST users than in cigarette smokers, although direct comparisons are limited. As an example, when comparing the results from two independent randomized placebo-controlled trials of bupropion-sustained release (the first in cigarette smokers and the more recent in ST users), higher abstinence rates were reported at the 6-week, 3-month, and 6-month time points for ST users as compared with results observed in cigarette smokers for both the placebo and the treatment condition. Briefly, for the placebo control condition, point-prevalence abstinence rates were 19%, 14%, and 15.7% in smokers (Hurt et al., 1997), and 38%, 26%, and 29% in ST users (Dale et al., 2002). Consistent with the Fagerström and Eissenberg review, these two independent placebo-controlled trials of bupropion-sustained release for smoking cessation and for ST cessation suggest that ST users have less “difficulty quitting” (Dale et al., 2002) (Hurt et al., 1997). In addition, Zhu et al. (2009) reported that the ST quit rate in men is three times the rate of quitting cigarettes (38.8% vs. 11.6%,  $p < 0.001$ ). These findings suggest that ST may have lower dependence potential than cigarettes.

##### **7.5.2-1.6.7.2. Behavioral Interventions**

The majority of controlled studies have shown that behavioral interventions increased abstinence rates relative to no or limited intervention in ST users (Burton et al., 2009; Hebert H. Severson, Andrews, Lichtenstein, Danaher, & Akers, 2007; Herbert H. Severson et al., 2009; M. Walsh et al., 2003; M. M. Walsh et al., 2010) ( $n = 60\text{--}3,072$ ). For example, Walsh et al. (2003) reported that at 1-year after intervention, past 30-day self-reported abstinence of 1,084 exclusive ST users (high school baseball athletes) was significantly greater in the

intervention group (27 percent) than in the control group (14 percent, OR = 2.29, 95 percent CI: 1.36–3.87).

Few studies have reported on the effect of the same intervention in ST users and smokers. In a study of tobacco-using high school students (including 42 ST users and 184 smokers), results after a behavioral intervention found that ST users, but not smokers, were more likely than controls to maintain cessation for 4 months (43.8% of ST users vs. 19.7% smokers (Burton et al., 2009)). In a study of 60 military personnel who were tobacco users, exclusive ST users (46%) were more likely to quit after a behavioral intervention relative to exclusive smokers (3%) and dual users (6%) ( $p < 0.01$ ; (Morgan, 2001)).

Overall, these data further support the conclusions drawn by Fagerström and Eissenberg (K. Fagerstrom & Eissenberg, 2012) that ST may have lower dependence potential than cigarettes.

#### 7.5.2-1.6.7.3. Nicotine Replacement Therapy

NRTs have also been investigated as possible interventions to promote ST cessation. NRTs have been shown to increase cigarette abstinence (Stead et al., 2012), and in highly dependent cigarette smokers, higher doses of NRT are more effective than lower doses in cessation (Kornitzer, Kittel, Dramaix, & Bourdoux, 1987; Tonnesen, 1988). In contrast to studies in smokers, the effectiveness of NRT such as the transdermal nicotine patch, nicotine gum or nicotine lozenges has been less consistently demonstrated in ST users. Studies with cigarette smokers have generally found a treatment outcome advantage for nicotine gum over placebo (K. O. Fagerstrom, 1988; Hughes et al., 1991). While shown to decrease withdrawal symptoms, both nicotine lozenges and nicotine gum have shown minimal benefit in promoting abstinence in ST users, particularly when the NRT is given in conjunction with behavioral therapy ((Jon O. Ebbert, Edmonds, Luo, Jensen, & Hatsukami, 2010; Jon O. Ebbert et al., 2009; Jon O. Ebbert, Severson, Croghan, Danaher, & Schroeder, 2010, 2013; D. Hatsukami, Jensen, Allen, Grillo, & Bliss, 1996);  $n = 60$ –402 subjects). The transdermal nicotine patch has, however, shown to significantly improve abstinence rates and reduce withdrawal symptoms in ST users as compared with placebo (Jon O. Ebbert, Croghan, et al., 2013; D. Hatsukami et al., 2000). It has been suggested that, because of the similarities in the rate of absorption and PK profile of orally administered NRTs and ST (Benowitz et al., 1988), nicotine gum or lozenges may produce a "priming effect" that facilitates lapses and relapse in ST users (D. Hatsukami et al., 1996).

#### 7.5.2-1.6.7.4. Pharmacotherapies

The efficacy of bupropion and varenicline in tobacco cessation has been evaluated in both cigarette smokers and ST users. Bupropion (300 mg/day) increased 3-month abstinence rates in ST users as compared with that for placebo, but this did not reach statistical significance in this small sample of 68 adult ST users (44% vs. 26%,  $p = 0.064$ ) and was not sustained for up to 6 months (29% for both groups; (Dale et al., 2002). In comparison, bupropion (300 mg/d) significantly increased abstinence rates in cigarette smokers at 3 months (25% vs. 14%,  $p < 0.05$ ) and 6 months (19% vs. 11%,  $p < 0.05$ ; Source: ZYBAN® package insert (GlaxoSmithKline, 2016)).

The efficacy of varenicline was assessed in two pilot studies of ST users. One study observed notable reductions in ST use ( $\geq 50\%$  reduction in 60% of subjects) and a 3-month abstinence rate of 15% in 20 ST users not interested in quitting (Jon O. Ebbert, Croghan, et al., 2010). A pilot study in 76 male adult treatment-seeking ST users showed that varenicline increased ST abstinence relative to placebo at 3 months (57.9% vs. 42.1%,  $p = 0.084$ ) and maintained it at 6 months (57.9% vs. 31.6%,  $p = 0.011$ ), although no differences were observed in abstinence from all tobacco products (Jon O. Ebbert, Croghan, Severson, Schroeder, & Hays, 2011). In comparison, varenicline has been shown to significantly increase abstinence in cigarette smokers relative to that for placebo at 9 to 12 weeks (44-51% vs. 12%-18%, depending on the study), and up to 1 year (19%-23% vs. 4%-10%; Source: (Saitta, Ferro, & Polosa).

Similar to the observed population differences in overall cessation rates, the cessation rates in these pharmacotherapy trials were generally higher in ST users than in cigarette smokers.

#### **7.5.2-1.6.7.5. Tobacco-Free Products**

While NRT has been demonstrated to alleviate withdrawal symptoms and cravings and to promote abstinence from ST use, other factors, such as sensory features of tobacco use behavior (e.g., tactile handling of can including tapping of the can, smell of the tobacco etc.), have been shown to alleviate withdrawal symptoms (but not craving) associated with ST abstinence (e.g., (Dennis E. McChargue et al., 2002)). Such findings are similar to previous reports in cigarette smokers, where the provision of smoking-related sensory stimuli has been observed to facilitate abstinence (Behm, Schur, Levin, Tashkin, & Rose, 1993; Rose et al., 1993; Westman, Behm, & Rose, 1995). In one study, the use of tobacco-free snuff provided as a cessation aid resulted in significantly lower mean carcinogen exposure ( $p < 0.01$ ), a significantly higher percentage of subjects achieving at least a 50 percent reduction in cotinine ( $p < 0.05$ ) at the end of treatment, a greater percentage of quit attempts ( $p < 0.05$ ), and a longer mean duration of abstinence in 106 adult ST users not interested in quitting ( $p < 0.05$  (D. K. Hatsukami et al., 2008)). The amount of tobacco reduction was similar to that found in studies of reduction interventions with cigarette smokers (D. Hatsukami et al., 2005).

#### **7.5.2-1.6.7.6. Combination Therapies**

In one study that implemented an 8-day residential treatment program, cessation-seeking ST users were able to utilize both nicotine patch and nicotine gum, as well as other pharmacotherapies if needed (i.e., bupropion). In this study, self-reported abstinence rates at 6 months were 87 percent, and biochemically confirmed abstinence rates at 1 year after treatment were 50 percent in 24 adult treatment-seeking ST users (J. O. Ebbert et al., 2004). This is higher than the self-reported abstinence rates reported in cessation-seeking smokers in a similar residential program (52 percent at 6 months after treatment (Hays et al., 2001)).

Table 7.5.2-1-7 provides a summary of the key results of each identified study related to ST cessation.

**Table 7.5.2-1-7: Literature Evaluating Smokeless Tobacco Cessation**

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
<b>Surveys</b>					
(Daughety et al., 1994)	Surveying smokeless tobacco use, oral lesions and cessation among high school boys	Cross-sectional. Survey  N = 183 experienced high school ST users (use >20 times) (Iowa)	Lifetime quit attempts	34% reported one or more attempts  Percent who attempted to quit lower than previous reports in adult ST users (68%; (H. H. Severson, Eakin, Lichtenstein, & Stevens, 1990))	<i>Limitations:</i> Cross-sectional Limited geographical generalizability Self-report - recall bias
(Jon O. Ebbert et al., 2005)	A survey of characteristics of smokeless tobacco users in a treatment program	Cross-sectional. Survey  N = 162 current ST users who underwent treatment (counseling/ pharmacological) (Minnesota)	Self-reported abstinence at ~ 2 years after treatment	37% ST abstinent  59% smoking abstinent  31% all tobacco abstinent	<i>Strengths:</i> Evaluated long-term abstinence rate (2 years)  <i>Limitations:</i> Cross-sectional design Small sample size; limited geographical generalizability Lack of information on treatment effective for maintaining abstinence Self-report No biochemical verification of abstinence

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
Behavioral Interventions							
(Burton et al., 2009)	Outcome of a tobacco use cessation randomized trial with high-school students	Randomized controlled trial of 2 cessation interventions (brief group sessions)  N = 337 high school students N = 184 smokers N = 42 ST users (California, Illinois)	Self-reported abstinence at 4 months  Salivary cotinine concentrations	ST users self-reported abstinence at 4 months: 14.3% vs. 0% (control - no intervention)  Smokers self-reported abstinence at 4 months: 6.5% vs. 3.2% (control - no intervention)  ST users less dependent on tobacco than smokers and were more likely to report abstinence at 4-month follow-up.  Overall dependency score did not predict ST use cessation, but lower scores on social influences associated with higher likelihood of quitting and maintaining abstinence at 4 months (p < 0.001).			Strengths: Randomized controlled trial Large sample size Biochemically verified abstinence at follow-up  Limitations: High attrition rate
(M. Walsh et al., 2003)	Spit (smokeless) tobacco intervention for high school athletes: Results after 1 year	Cluster-randomized controlled trial of behavioral intervention vs. no intervention  N = 1,084 high school baseball athletes using ST (rural California)	Quit rate (1 year)	Quit rate:	Intervention 27%	Control 14%	Strengths: Randomized treatment assignment Large sample size  Limitations Self-report No biochemical verification of abstinence Limited geographic and age generalizability
(M. M. Walsh et al., 2010)	Smokeless tobacco cessation cluster randomized trial with rural high school males: Intervention interaction with baseline smoking	Cluster-randomized controlled trial of behavioral intervention vs. no intervention  N = 3,072 high school male students (rural California)	Past 30-day cessation (1 year)	ST users: Dual users:	Intervention 62% 51%	Control 36% (p < 0.001) 56% (p = 0.740)	Strengths: Longitudinal
				Frequency of ST use predicted quitting, with less frequent users more likely to quit than daily users, independent of condition.			Limitations: Self-report Limited geographical generalizability

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
(Danaher et al., 2013)	Randomized controlled trial of MyLastDip: A web-based smokeless tobacco cessation program for chewers ages 14-25	Randomized trial of 2 web-based ST cessation interventions (basic and enhanced)  N = 1,716 treatment-seeking adolescents and young adults (United States [97.5%], Canada)	Self-reported abstinence (3- and 6-months combined)	All tobacco: ST:	<i>Enhanced</i> 28.9% 35.2%	<i>Basic</i> 25.6% 32.2%	<i>Strengths:</i> Large sample size Prospective evaluation Geographically diverse Real-world assessment of intervention Longitudinal assessment Good retention (71% at 6 months)  <i>Limitations:</i> Self-report No biochemical verification of abstinence
				ST only users more likely to quit after behavioral intervention vs. no intervention.  ST use intensity and time to first use were not predictive of quitting.			
(Hebert H. Severson et al., 2007)	Self-help cessation programs for smokeless tobacco users: Long-term follow-up of a randomized trial	Randomized trial of two self-help conditions (manual only or assisted self-help)  N = 1,069 treatment-seeking ST users (Oregon, Washington, Idaho, Montana, Alaska)	Self-reported abstinence	All tobacco:  6 months: 12 months: 18 months:	<i>Manual only</i>  23.1% 24.9% 22.6%	<i>Assisted self-help</i>  31.5% (p < 0.05) 26.9% 26.7%	<i>Strengths:</i> Randomized Large sample size Long-term follow-up  <i>Limitations:</i> Self-report No biochemical verification of abstinence High attrition
				Assisted self-help increased cessation rate at 6 months, but not at 12-month follow-up, related to increases in quitting in manual only group and decreased abstinence in assisted self-help group; however, assisted self-help group consistently showed greater abstinence over time.			
(Morgan, 2001)	Evaluation of an educational intervention for military tobacco users	Single-arm trial of a brief intervention on tobacco use and cessation  N = 60 military tobacco users N = 31 smokers N = 13 ST users (Kentucky)	Self-reported tobacco use at 1 month	Abstinence: Decreased use: Intent to quit (contemplation/preparation/action):	<i>ST users</i> 46% 15%  15%/31%/46%	<i>Smokers</i> 3% 50%  39%/39%/3%	<i>Limitations:</i> Small sample size Limited generalizability to general population Self-report No biochemical verification of abstinence No control group Limited follow-up to evaluate abstinence
			Intention to quit	ST users showed most significant behavior change after the intervention.			

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
				Most ST users either quit or were in the action stage of intent to quit, whereas most smokers continued to smoke and were more likely to be in the contemplation and preparation stages of intent to quit.			
(Herbert H. Severson et al., 2009)	Smokeless tobacco cessation in military personnel: A randomized controlled trial	Randomized controlled trial of behavioral intervention vs. usual care  N = 785 military ST users (U.S.)	Self-reported abstinence	All tobacco:	Behavioral	Usual care	Strengths: Randomized treatment assignment Moderate sample size  Limitations: Limited generalizability Self-report No biochemical verification of abstinence High attrition
				3 months:	29.1%	10.4% (p < 0.001)	
				6 months:	29.3%	14.0% (p < 0.001)	
				ST abstinence:			
				3 months:	26.0%	10.7% (p < 0.001)	
				6 months:	16.8%	6.4% (p < 0.001)	
				Behavioral intervention resulted in 2-3 times greater abstinence vs. usual care condition.			
				Increasing age, dependence and desire to quit were significant predictors of abstinence.			
Nicotine Replacement Therapy							
(Jon O. Ebbert et al., 2009)	A randomized clinical trial of nicotine lozenge for smokeless tobacco use	Randomized, double-blind, placebo-controlled trial of nicotine lozenge (4 mg/lozenge)  N = 270 adult treatment-seeking ST users (Minnesota, Oregon)	Self-reported all tobacco and ST abstinence at 12 weeks  Urine anabasine concentrations	All tobacco:	Lozenge	Placebo	Strengths: Randomized controlled trial Biochemical verification of tobacco abstinence  Limitations: Technical difficulties with biochemical assay disconfirmed multiple urine samples Compliance issues
				Cotinine-verified:	36%	27.6% (p = 0.138)	
				Self-report:	44.1%	29.1% (p = 0.011)	
				ST abstinence:			
				Self-report:	50.7%	34.3% (p = 0.013)	
				Nicotine lozenge associated with increased self-reported, but not biochemically verified, tobacco abstinence at 12 weeks.			
				Nicotine lozenge associated with reductions in withdrawal symptoms and tobacco craving.			



Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
(Jon O. Ebbert, Severson, et al., 2010)	A pilot study of mailed nicotine lozenges with assisted self-help for the treatment of smokeless tobacco users	Randomized, placebo-controlled trial of behavioral intervention and nicotine lozenge (4 mg)  N = 60 treatment-seeking ST users (Minnesota, Oregon)	Self-reported abstinence	Abstinence:	<i>Lozenge+ behavioral</i>	<i>Placebo+ behavioral</i>	<i>Strengths:</i> Randomized controlled trial  <i>Limitations:</i> Small sample size Self-report No biochemical verification of abstinence
				12 weeks: 6 months:	47% 33%	37% (p = 0.432) 47% (p = 0.292)	
				Mailing nicotine lozenges did not significantly increase abstinence as compared with behavioral intervention alone, but was more effective in alleviating withdrawal than the placebo lozenge.			
(Jon O. Ebbert, Edmonds, et al., 2010)	Smokeless tobacco reduction with the nicotine lozenge and behavioral intervention	Randomized, open-label pilot study of behavioral intervention alone or with nicotine lozenge (4 mg)  N = 102 adult ST users not interested in quitting (Minnesota)	% of subjects who reduced ST use by ≥ 75% at 8 weeks  All tobacco abstinence at 8 weeks	Reduction:	<i>Lozenge+ behavioral</i>	<i>Behavioral</i>	<i>Strengths:</i> Randomized Biochemical verification of tobacco abstinence  <i>Limitations:</i> Small sample size No placebo lozenge or counseling control No titration of lozenge dosing based on ST use
				Abstinence:	32.1% 14.0%	16.7% (p = 0.08) 6.7% (p = 0.34)	
				Similar increase in self-reported abstinence over time for both groups, but no group differences on any of the measures evaluated.			
(Jon O. Ebbert, Severson, et al., 2013)	Comparative effectiveness of the nicotine lozenge and tobacco-free snuff for smokeless tobacco reduction	Randomized trial of nicotine lozenge (4 mg) vs. tobacco-free snuff  N = 81 adult ST users not interested in quitting (Minnesota, Oregon)	% of subjects who reduced ST use by ≥ 50% at 4, 8, 12, and 26 weeks  Self-reported abstinence/urine cotinine concentrations	<i>Reduction:</i>	<i>Lozenge</i>	<i>Snuff</i>	<i>Strengths:</i> Biochemical verification of tobacco abstinence  <i>Limitations:</i> Small sample size Open-label
				4 weeks: 8 weeks: 12 weeks: 26 weeks:	62% 60% 55% 50%	46% (p = 0.108) 61% (p = 0.624) 66% (p = 0.890) 54% (p = 0.709)	
				Abstinence:	20%	12% (p = 0.257)	
				No difference in ST use reduction or abstinence rates between lozenge and tobacco-free snuff groups of users who do did not intend to quit.			
				Nicotine withdrawal similar in both groups.			



Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
(Jon O. Ebbert, Croghan, et al., 2013)	A randomized Phase II clinical trial of high-dose nicotine patch therapy for smokeless tobacco users	Randomized, double-blind, placebo-controlled trial of nicotine patch (42 mg/day)  N = 52 adult ST users (Minnesota)	Self-reported all tobacco abstinence at 8 weeks, 3 months and 6 months  Urine anabasine concentrations	All tobacco: 8 weeks: 3 months: 6 months:	Patch 44% 48% 44%	Placebo 22% (p = 0.05) 19% (p = 0.014) 26% (p = 0.087)	Strengths: Randomized controlled trial Biochemical verification of tobacco abstinence
				High-dose nicotine patch increased tobacco abstinence at end-of-treatment (8 weeks) and 3 months, and was associated with decreased nicotine withdrawal.			Limitations: Small sample size
(D. Hatsukami et al., 2000)	Treatment of spit tobacco users with transdermal nicotine system and mint snuff	Randomized, controlled trial of nicotine patch or mint snuff  N = 402 adult treatment-seeking ST users (Minnesota)	Self-reported abstinence Anabasine/ anatabine concentrations	Abstinence: 10 weeks 62 weeks	Patch+snuff 72% 35%	Patch+no snuff 61% 32%	Strengths: Randomized Placebo control Biochemical verification of abstinence
				Abstinence: 10 weeks 62 weeks	Placebo+snuff 51% 27%	Placebo+no snuff 55% 33%	
				Nicotine patch increased short-term abstinence rate (10 weeks, p = 0.006) as compared with that for placebo patch and reduced craving and withdrawal symptoms.  Mint snuff did not impact treatment outcome, but reduced craving and withdrawal symptoms.			Limitations: Self-reported use of mint snuff Limited generalizability to lighter ST users and dual users

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings			Comments
(D. Hatsukami et al., 1996)	Effects of behavioral and pharmacological treatment on smokeless tobacco users	Randomized, placebo-controlled trial of behavioral intervention or nicotine gum (2 mg)  N = 210 adult treatment-seeking ST users (Minnesota)	Self-reported abstinence at 4 weeks, and 1-month and 6-month follow-up  Salivary cotinine concentrations	<p>Abstinence:</p> <p>4 weeks 1 and 6 months follow-up</p> <p>Abstinence:</p> <p>4 weeks 1 and 6 months follow-up</p> <p>Based on survival analysis, abstinence similar for all groups except for the no behavioral intervention and placebo gum group.</p> <p>At Week 4, odds of abstinence 2.5 times greater for behavioral intervention vs. no behavioral intervention. At 6-month follow-up, odds of abstinence 2.5 times greater for behavioral intervention + gum vs. other 3 groups.</p> <p>Nicotine gum at 2-mg dose level not found to be more successful than placebo.</p>	<p><i>Behavioral+ Gum</i></p> <p>63.6% 45.5%/47.3%</p> <p><i>No behavioral +Gum</i></p> <p>35.3% 21.6%/19.6%</p>	<p><i>Behavioral+No gum</i></p> <p>66.0% 50.0%/28.0%</p> <p><i>No behavioral +No gum</i></p> <p>48.1% 33.3%/31.5%</p>	<p><i>Strengths:</i> Randomized Placebo control</p> <p><i>Limitations:</i> Small sample size Nicotine gum dose possibly too low Cotinine as biochemical verification for study involving NRT limits confirmation of true abstinence</p>
<b>Pharmacotherapy</b>							
(Dale et al., 2002)	Bupropion for the treatment of nicotine dependence in spit tobacco users: a pilot study	Randomized, double-blind, placebo-controlled trial of bupropion (300 mg/d)  N = 68 adult ST users (Minnesota)	Self-reported abstinence  Salivary cotinine concentrations	<p>Abstinence at:</p> <p>12 weeks: 24 weeks:</p> <p>Bupropion may increase abstinence rates in ST users; and may also reduce severity of withdrawal symptoms and reduce weight gain during abstinence.</p>	<p>Bupropion:</p> <p>44% 29%</p>	<p>Placebo:</p> <p>26% (p = 0.064) 29%</p>	<p><i>Strengths</i> Randomized controlled trial Biochemical verification of abstinence</p> <p><i>Limitations:</i> Small sample size High attrition</p>

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
(Jon O. Ebbert, Croghan, et al., 2010)	A pilot study to assess smokeless tobacco use reduction with varenicline	Single-arm trial of varenicline (2 mg/day)  N = 20 male adult ST users not interested in quitting (Minnesota)	% of subjects who reduced ST use by ≥ 50% at 12 weeks and 6 months  Self-reported abstinence/ urine cotinine concentrations	Reduction: 12 weeks: 6 months:	Varenicline 60% 50%		Strengths: Biochemical verification of tobacco abstinence  Limitations: Small sample size Open-label Use of unvalidated scale
				Abstinence: 12 weeks: 6 months:	15% 10%		
				Varenicline associated with reduction in ST use and craving among users who did not intend to quit.			
(Jon O. Ebbert et al., 2011)	A pilot study of the efficacy of varenicline for the treatment of smokeless tobacco users in Midwestern United States	Randomized, double-blind, placebo-controlled trial of varenicline (2 mg/day)  N = 76 male adult treatment-seeking ST users (Minnesota, Wisconsin)	Self-reported all tobacco and ST abstinence at 12 weeks and 6 months  Urine cotinine concentrations	All tobacco abstinence: 12 weeks: 6 months:	Varenicline 55.3% 47.4%	Placebo 42.1% (p = 0.126) 31.6% (p = 0.080)	Strengths: Randomized controlled trial Biochemical verification of tobacco abstinence  Limitations: Small sample size
				ST abstinence: 12 weeks: 6 months:	57.9% 57.9%	42.1% (p = 0.084) 31.6% (p = 0.011)	
				Overall, higher point prevalence abstinence rates with varenicline than with placebo, although not statistically significant for all tobacco abstinence, and only significant at 6 months for ST only.  Craving significantly lower with varenicline than with placebo.			

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors' Findings			Comments
(K. Fagerstrom & Eissenberg, 2012)	Dependence on tobacco and nicotine products: A case for product-specific assessment	Reanalysis of tobacco cessation trials (placebo groups)	Success rate in placebo group as proxy of difficulty abstaining	<p>Smokers: 10% (range: 9.8-11.2%) ST users: 25% (range: 19.1-33.0) NRT (gum): 36%</p> <p>Difficulty quitting cigarettes greater than quitting ST Dependence differs across tobacco/nicotine products, with dependence on NRT lowest, leading to more successful cessation, and dependence on cigarettes highest; ST in between. Authors posit a continuum of dependence across various tobacco products.</p> <p>Recommend use of product-specific instruments to assess dependence.</p>			<p><i>Strengths:</i> Review of multiple controlled intervention trials</p> <p><i>Limitations:</i> Follow-up periods varied (e.g., 6 months for most ST trials vs. 1 year for NRT trial)</p>
Tobacco-free Intervention							
(D. K. Hatsukami et al., 2008)	Smokeless tobacco reduction: Preliminary study of tobacco-free snuff versus no snuff	Randomized trial of tobacco-free snuff or no snuff  N = 106 adult ST users not interested in quitting (Minnesota)	ST reduction at 4, 8 and 12 weeks % of subjects who reduced ST use by ≥ 50%  Self-reported abstinence  Urine cotinine concentrations  Duration of abstinence	Reduction (tins/week):  Week 4: Week 8: Week 12:  Abstinence: Week 12: Duration (days):  Among ST users not interested in quitting, ST use decreased over time similarly independent of snuff condition.  Magnitude of reduction similar to that in studies in smokers (e.g., Hatsukami et al. 2005), but abstinence rate may be higher than that in smokers receiving medicinal nicotine (6%-8%).  Tobacco-free snuff may facilitate long-term abstinence by duration of abstinence and increasing the number of quit attempts.	Tobacco-free snuff  48.1% 71.2% 34.3%  34.2% 22.6	No snuff  50.0% 57.4% 25.9%  14.6% (p = 0.030) 10.7 (p = 0.026)	<p><i>Strengths:</i> Biochemical verification of abstinence</p> <p><i>Limitations:</i> Small sample size High attrition</p>
Combination Therapy							

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings			Comments
(J. O. Ebbert et al., 2004)	Residential treatment for smokeless tobacco use: a case series	Single-arm trial of 8-day treatment program including behavioral treatment, nicotine patch/gum and bupropion  N = 24 adult treatment-seeking ST users (Minnesota)	Self-reported continuous abstinence at 3, 6, and 12 months  Urine anabasine concentrations (12 months only)	All tobacco abstinence: 3 months: 6 months: 12 months:	92% 87% 50%		<i>Strengths:</i> Individualized treatment Combined therapy approach Biochemical verification of abstinence  <i>Limitations:</i> Small sample size Observational No control Could not evaluate individual treatment components Missing baseline information
(Schiller et al., 2012)	Comparing an immediate cessation versus reduction approach to smokeless tobacco cessation	Randomized trial of immediate cessation + patch and ST reduction+ lozenge/ST brand switch  N = 199 ST users not interested in quitting (Minnesota)	Self-reported abstinence  ST use reduction  Carbon monoxide, cotinine, anatabine concentrations	ST use reduction: (dips per day) (baseline to Week 6)  Abstinence: 12 weeks: 26 weeks:	<i>Immediate cessation</i> 7.5 to 0.6 dips per day  31% 21%	<i>ST use reduction</i> Switch: 8.2 to 4.7 dips per day Lozenge: 6.9 to 1.3 dips per day  17% 10%	<i>Strengths:</i> Randomized treatment assignment Biochemical verification of abstinence  <i>Limitations:</i> Substantial attrition
				ST users not interested in quitting more successful in maintaining abstinence with immediate cessation vs. reduction approach			
				ST use reduced during treatment and follow-up			

#### 7.5.2-1.6.8. Nonclinical Abuse Potential

The MRTPA 2012 Draft Guidance recommends that information be included on nonclinical studies related to abuse potential of tobacco products to evaluate the discriminative stimulus effects and threshold doses of nicotine/tobacco products that may produce reinforcing effects. An abundance of nonclinical evidence already exists for nicotine, the primary psychoactive constituent in tobacco products (De Biasi & Dani, 2011; Donny, Caggiula, Weaver, Levin, & Sved, 2011). However, nonclinical studies have limited external validity or translational value in the case of whole tobacco products. Researchers would have difficulty emulating product use conditions in animals (e.g., training animals to hold a dip in their mouths). Moreover, interspecies differences in nicotine metabolism, dosing regimen, and receptor pharmacology limit translation of such information for a given tobacco product (e.g., (Caille, Clemens, Stinus, & Cador, 2012; Matta et al., 2007; O'Dell & Khroyan, 2009)). For these reasons, the primary approach to abuse potential assessment for the purpose of this MRTPA does not include dedicated nonclinical testing of ST, but rather a summary of the available nonclinical literature on tobacco extracts. Section 7.5.2-1.6.8 briefly describes the literature. Although nonnicotine constituents possess some pharmacological activity, overall, the literature on tobacco extracts supports that nicotine is the primary pharmacological determinant of tobacco's abuse potential.

A few studies have shown that some nonnicotine tobacco constituents exhibit pharmacological activity related to abuse potential. For example, acetaldehyde and nornicotine function act as positive reinforcers in animal intravenous self-administration models (Bardo, Green, Crooks, & Dwoskin, 1999; Caine et al., 2014; Peana, Muggironi, & Diana, 2010). In addition, the interoceptive effects of well-tolerated doses of anatabine, anabasine, and nornicotine, minor alkaloids that are substantially less potent (10 to 100 times less) than nicotine, overlap with nicotine (0.32 mg/kg, intraperitoneally) in animal drug discrimination substitution assays. However, anatabine and anabasine do not maintain self-administration, indicating these have no reinforcing efficacy (Caine et al., 2014).

Tobacco smoking is thought to have antidepressant effects through monoamine oxidase-inhibiting properties of nonnicotine constituents (Balfour & Ridley, 2000). Thus, in addition to tobacco's reinforcing effects, its antidepressant properties may contribute to continued use. Alford et al. (Alford et al., 2006) evaluated whether ST can also inhibit monoamine oxidase; results demonstrated that ST extract does not produce monoamine oxidase inhibition in frontal cortex of rats, and thus, this is unlikely to contribute to the reinforcing effects of ST.

The behavioral pharmacologic effects of nicotine alone and nicotine delivered via ST extract have also been evaluated in rats (Andrew C. Harris, Stepanov, Pentel, & Lesage, 2012; A. C. Harris et al., 2015). In Harris et al. (2012), nicotine alone and in ST extract form (Kodiak ST) lowered intracranial self-stimulation [ICSS] thresholds (i.e., enhanced reinforcement) to a similar degree at low to moderate (0.06 to 0.5 mg/kg, subcutaneous) doses. At a higher dose, nicotine alone (0.75 mg/kg, subcutaneous) increased ICSS thresholds (indicative of diminished reinforcement), whereas ICSS thresholds remained lower for nicotine in ST extract (0.75, 1.25 mg/kg, subcutaneous). Nicotine alone and in ST extract resulted in similar

brain nicotine accumulation levels and locomotor stimulant effects; however, the nicotine in ST extract did not substitute as fully as nicotine alone in a drug discrimination procedure. In [Harris et al. \(2015\)](#), low to moderate doses of nicotine lowered the minimal (threshold) stimulation intensity that maintains ICSS, and acute ST extract (Kodiak® ST and Camel® snus) subcutaneous injection produced reinforcement-enhancing (ICSS threshold-decreasing) effects similar to those of nicotine alone (low-moderate doses), as well as similar aversive (ICSS threshold-increasing) effects seen at the high nicotine doses. The above results indicate that ST extract has reinforcing properties that are similar to those observed for nicotine alone at low to moderate doses, suggesting that the nonnicotine constituents in ST do not significantly contribute to its abuse potential. These findings are in contrast with studies of tobacco smoke extracts/cocktails, in which the nonnicotine constituents enhanced nicotine self-administration ([Brennan et al., 2015](#); [Clemens, Caille, Stinus, & Cador, 2009](#); [Costello et al., 2014](#)).

[Table 7.5.2-1-8](#) presents a summary of the nonclinical studies related to the abuse potential of ST.

**Table 7.5.2-1-8: Literature Evaluating Nonclinical Abuse Potential of Smokeless Tobacco**

Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(A. C. Harris et al., 2015)	Animal models to assess the abuse potential of tobacco products: Effects of smokeless tobacco extracts on intracranial self-stimulation	ICSS animal model  N = 10-12 rats per experiment	ICSS thresholds	Kodiak extract, Camel snus extract and nicotine alone produced a similar dose-dependent effect on ICSS thresholds; decreasing thresholds at lower doses (reinforcing) and increasing at higher doses (aversion)  Relative nicotine content is primary pharmacologic determinant of reinforcing effects of ST products, as measured by ICSS	<i>Strengths:</i> Extract provides more relevant exposure levels than isolated constituents used in previous studies Two ST products evaluated  <i>Limitations:</i> Separate experiments do not permit direct comparison between Camel snus and Kodiak Acute effects comparison does not reflect potential effect of nonnicotine constituents after repeated ST exposure
(Andrew C. Harris et al., 2012)	Delivery of nicotine in an extract of a smokeless tobacco product reduces its reinforcement-attenuating and discriminative stimulus effects in rats	ICSS Drug discrimination Locomotor activity  N = 8-24 per experiment	ICSS thresholds  % active lever responding  Locomotion	ST extract and nicotine alone produced a similar threshold-decreasing (reinforcing) effect at low doses (0.06-0.5 mg/kg), and increase (aversion) at moderate dose of nicotine only (0.75 mg/kg).  Lower substitution for nicotine with moderate doses of ST extract than with nicotine alone, indicating rightward shift in dose-response curve.  ST extract and nicotine alone produced similar locomotor enhancing effects.  Nonnicotine constituents may reduce some of nicotine's behavioral effects.	<i>Limitations:</i> Rats not experimentally naïve



Author Publication Year	Title	Study Type Sample	Measures	Outcomes and Authors’ Findings	Comments
(Alford et al., 2006)	Effect of smokeless tobacco extract on catecholamine metabolic enzymes in rat brain: "Dippers" are getting only half of the bang	Radio-immunoreactivity assays  N = 140 rats	TH and MAO activity after acute and chronic ST extract administration	<p>40 and 160 mg/kg ST extract significantly increased TH in the LC after 14 and 28 (40 mg/kg only) days chronic administration, but did not alter MAO activity after 1, 14, or 28 days.</p> <p>ST does not have MAO-inhibiting properties, unlike smoked tobacco ST does not decrease TH in LC, unlike antidepressants.</p> <p>Authors conclude that ST reinforcing effects result entirely from nicotine's direct dopaminergic and noradrenergic actions.</p>	<p><i>Strengths:</i> Nicotine in ST at behaviorally relevant doses</p> <p><i>Limitations:</i> No direct comparison to smoked tobacco</p>

#### 7.5.2-1.6.9. Summary

- Reports of ST use outside of “normal use” (i.e., placement in the oral cavity) are very rare.
- Trends in age at initiation, as well as motivations to initiate use appear to be similar for ST and cigarettes (e.g., (Ary et al., 1989)). However, trial and initiation of ST use are significantly lower than that of cigarette smoking, and males are more likely than females to initiate ST use, whereas initiation of cigarette smoking is, for the most part, comparable across sex (Section 7.5.3.1).
- Although a limited number of studies have been conducted, controlled randomized crossover clinical laboratory studies support that acutely administered ST products have detectable subjective effects, as seen by significant increases on subjective measures of nicotine effects (e.g., strength of product, alertness, stimulation, heart racing) and decreases in urge/craving after administration. In contrast with studies evaluating only ST products, research with multiple tobacco/nicotine products has shown that large differences in nicotine exposure (e.g., slower absorption with ST than with cigarettes) are associated with large differences in subjective response and that the relative abuse potential of loose ST is, as expected, lower than that of cigarettes and on several measures, higher than that of NRT.
- Abstinence from ST results in withdrawal signs and symptoms similar to those reported in smokers; however, the magnitude of withdrawal appears to be lower in ST users. In smokers, ST suppresses withdrawal and craving less effectively than cigarettes; however, higher-nicotine-content products may be more effective in relieving craving.
- Based on the limited literature, the effect of nicotine dose in ST products on withdrawal symptom relief and craving remains inconclusive. The data also suggest that the relationship between nicotine exposure and an ST product’s likeability, ability to reduce cravings/urges and subjective effects is not linear. Lack of dose response may, in part, be related to the variability in exposure to nicotine (e.g., due to use behaviors, physical differences, genetic differences, pH), sensorial attributes of ST, and other factors.
- Despite differences in design, measures and population, the results of available studies examining dependence in ST users indicate that dependence varies as a function of amount/length of use. TTFU is a strong predictor of dependence, with ST users exhibiting a longer TTFU than cigarette smokers. Furthermore, the literature indicates that cotinine exposure may only have limited application in ST users as a dependence marker. In studies including both cigarette smokers and ST users, dependence in ST users appears to be similar to (three studies) or less than (three studies) that reported in cigarette smokers.
- Overall cessation rates appear to be higher in ST users than in cigarette smokers, suggesting a lower dependence potential. Tested interventions may be more effective in cigarette smokers; however, the small sample sizes in ST users have limited

statistical power, and there have been few direct comparisons across tobacco user types.

- Evidence from studies evaluating dependence and cessation of ST and cigarettes is consistent with that from Fagerström and Eissenberg ([K. Fagerstrom & Eissenberg, 2012](#)), who suggested that there exists a continuum of dependence for tobacco/nicotine products: “The cigarette seems to be in the high dependence end of this continuum, while NR [nicotine replacement] products, and particularly the patch, seemed to be positioned on the low end of the dependence continuum. ST appears to have an intermediate position on the dependence continuum.”
- Based on available nonclinical studies, nicotine content appears to be the primary pharmacological determinant of the abuse potential of ST products.

The available evidence suggests that the abuse potential of ST is higher or similar to that of NRT, but consistently lower than that of cigarettes.

## 7.5.2-1.7. Literature Cited

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