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Nicotine Reduction in Cigarettes: Literature Review and Gap Analysis

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Abstract

Background: The US Food and Drug Administration (FDA) is considering reducing nicotine levels in cigarettes to "minimally or non-addictive levels." However, important research gaps remain, and the FDA must determine when the available research is sufficient to support moving forward.
Methods: The authors conducted a systematic review of research articles in PubMed relating to nicotine reduction. Building on a review of risk assessment best practices, the authors also developed a risk assessment framework for tobacco regulation and used it to guide a gap analysis of nicotine reduction research.
Results: The final sample consisted of 78 articles. The majority examined either nicotine dependence on very low nicotine cigarettes (VLNCs) or markers of potential health effects of using VLNCs. One-third of the identified articles reported results from four large randomized controlled trials (RCTs). While these studies report promising results and suggest that a nicotine reduction rule would be a powerful tool to reduce cigarette smoking, our gap analysis suggests that there is a need for studies that better reflect the use and availability of a wide range of tobacco/nicotine products and the potential for dual- or multi-product use.
Conclusion: The current body of research on nicotine reduction is weighted towards RCTs, which is appropriate for a policy that has not yet been implemented anywhere in the world. The FDA must consider a wide range of factors that may impact a product standard's public health impact, including those difficult to assess in RCTs, such as a nicotine reduction rule's impact on smoking initiation and relapse.
Implications: This systematic review presents a gap analysis based on a risk assessment framework to help identify remaining research priorities to inform FDA's potential product standard to reduce nicotine levels in cigarettes. Quickly addressing those gaps would support the FDA's effort to develop a nicotine reduction product standard that will be effective and withstand legal challenges.

Introduction

Tobacco use remains the leading cause of preventable disease and death in the United States, with approximately 480 000 deaths occurring each year.[1] The 50th-anniversary report of the US Surgeon General in 2014 stated that although we have seen great success in tobacco control, progress is not moving fast enough, and rapid elimination of cigarettes and combusted tobacco is needed.[1] New regulatory strategies are needed to speed the progress of tobacco control.

Because of the inherent risk of tobacco products, the 2009 Family Smoking Prevention and Tobacco Control Act (TCA) requires the US Food and Drug Administration (FDA) to apply a "public health standard" when evaluating potential regulations. This standard includes assessment of risks and benefits to the population as a whole, including the increased or decreased likelihood of initiation and cessation of tobacco products.[2] Building on a previous analysis of risk assessment practices in the federal government,[3] as well as the work of the Tobacco Product Assessment Consortium,[4] we propose

a risk assessment framework (Figure 1) to characterize the anticipated effects of a new tobacco product standard. The framework builds upon the four-part risk assessment framework outlined in the National Research Council's "Red Book"[5] and "Silver Book,"[6] but it includes modifications and additions to account for some of the salient features of tobacco use and regulation. These include the important role of dependence, the different populations and tobacco use phases (initiation, cessation, relapse) specified in the TCA, the dynamic responses of the tobacco industry and consumers, and other factors.

At the center of the framework is the *exposure assessment*, which, in the language of risk assessment, refers to how much people (including, as appropriate, vulnerable populations and other subpopulations of interest) are exposed to the hazard at issue. We show in the framework that this level of exposure may be influenced by a variety of external factors, including:

- the availability and relative attractiveness of other nicotine products;
- the use of other substances that may act as partial substitutes or otherwise influence levels of use;
- tobacco industry marketing, public health "counter-advertising," and FDA educational efforts; and
- prices of the tobacco product at issue as well as possible alternatives.

This exposure assessment is then combined with the *effects assessment*, which looks at the physical effects of using the product being studied (the hazard assessment) at various doses (the dose-response assessment). Together, these pieces of the framework can be used to produce the *risk characterization*—a quantitative model of the potential harms (or public health benefits) of the product being reviewed. In modeling the health effects, a risk assessment conducted for purposes of tobacco regulation under the TCA should consider the specific factors referenced in the law (eg, effects on likelihood of initiation and cessation), in addition to overall effects on the health of the population.

As a test case, we apply this framework to a proposed product standard reducing the nicotine content in cigarettes, as it holds potential for a significant impact on public health.

As the burden of tobacco-related disease is primarily associated with cigarettes and combusted tobacco product use, the 2014 Surgeon General's Report identified reducing nicotine content to make cigarettes less addictive as a promising regulatory strategy,[1] and under the TCA's framework, this approach is legally viable.[7] Originally proposed by Benowitz and Henningfield in 1994,[8] this strategy aims to set a standard for nicotine content that would prevent cigarettes from being capable of causing addiction.[9] Previous literature reviews have determined that very low nicotine content cigarettes (VLNCs) (≤0.4 mg/g) reduce exposure to nicotine, smoking quantity, and dependence,[10] and increase the likelihood of contemplating, making, and succeeding at a quit attempt.[11] These reviews identified some gaps in the evidence base, including the effects of gradual compared with immediate changes in nicotine content and the effects on vulnerable populations, which we sought to reexamine in the current review.[10,11]

In July 2017, the FDA announced a comprehensive plan to regulate tobacco and nicotine. This framework emphasized the use of regulation to reduce nicotine levels in cigarettes and to ensure the availability of less harmful nicotine alternatives.[12] In March 2018, FDA published an Advance Notice of Proposed Rulemaking for public comment on a tobacco product standard for nicotine levels of combusted cigarettes.[13] As of this writing, the FDA has consistently

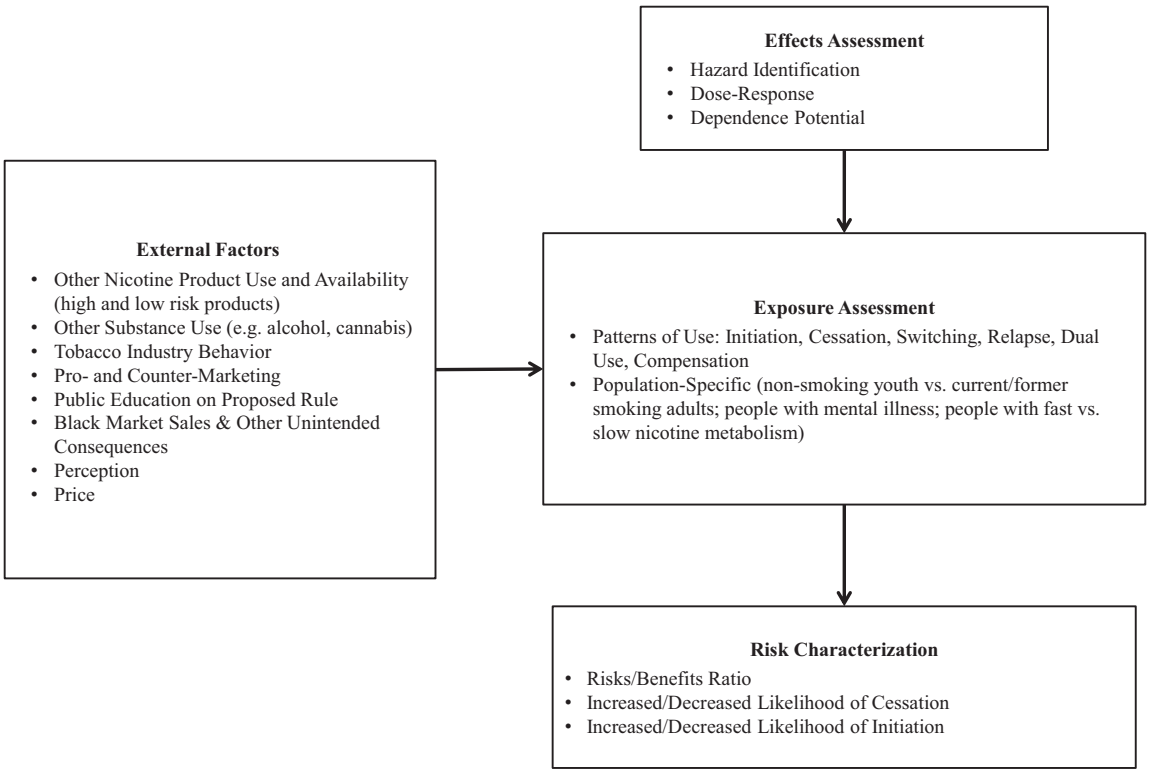

Figure 1. Risk assessment framework for evaluating a proposed product standard to reduce nicotine levels in cigarettes.

announced its intent to move forward with regulating nicotine levels in cigarettes, but no proposed rule has yet been issued.[14] The aim of this article is to, applying a risk assessment framework, systematically review the existing evidence and identify information gaps to guide future research and allow FDA to characterize the potential effects of nicotine reduction according to the public health standard.

Methods

Search Strategy

Databases and Keywords

A search of the published literature on reduced nicotine content cigarettes indexed in PubMed was conducted on September 4, 2018, using the following search terms: "reduced nicotine" OR "nicotine reduction" OR "low nicotine" OR "reducing nicotine" OR "very low nicotine" OR "nicotine regulation." A publication cut-off year of 2013 was chosen based on key informant recommendations to use the first year that 22nd Century's SPECTRUM government research cigarettes were first used in a published study (this may include studies conducted prior to 2013, such as those conducted with commercially-available Quest cigarettes, but published during 2013 or after). In addition, this cut-off date was designed to capture papers published following previous reviews on this topic.[10,11]

Abstract/Title and Full Text Review

Ineligible publication types included commentaries, editorials, letters to the editor, conference proceedings, research protocols, and reviews (although systematic reviews were retained for background and comparison). Other exclusion criteria included: study was not published in English, study was not relevant to reduced nicotine content cigarettes, and study was a duplicate of a study already included in this review.

Two coders (AMG, MB) screened the abstracts and titles of papers to move on to the full-text review phase. Again, these two coders screened the full-text articles for inclusion in the review. The two coders discussed discrepancies and came to an agreement.

Data Extraction

One author extracted the data (AMG), and one author double-checked extraction (MB). The following study characteristics were captured for synthesis: study type (human/animal/product/modeling), study topic (toxicity/health effects/dependence potential/patterns of use/perceptions/other), study design, sample size and inclusion criteria, products tested, study procedures, measures, results, limitations, and funding.

Results

Overall

Figure 2 presents a flow of articles from search to inclusion in this review. Table 1 presents the range of outcomes measured across the included studies.

Effects Assessment

In our framework, we have included two of the core steps of a traditional risk assessment—hazard assessment and dose-response assessment—within the broader category of "effects assessment." Most of the studies conducted to date focus on hazard, that is, the potential health effects (positive or negative) of VLNC use, and do not specifically model dose-related responses. A key goal of a nicotine reduction policy, of course, would be to reduce the addictiveness of cigarettes. Thus, we include dependence potential as a separate category within "effects assessment" and report on those studies below.

Health Effects

Health effects studies identified for inclusion consisted of laboratory animal studies (n = 2), laboratory product evaluation/smoking machine studies (n = 3), and human studies (n = 15).

Animal models are critical to tobacco-related research because they provide mechanistic information that may be relevant to humans. Importantly, they also provide a means of studying adolescents—the primary risk period for tobacco initiation—where analogous studies in humans are not ethical. Only two studies, both by Abreu-Villaca and colleagues, have looked at the potential health effects of VLNCs using animal models.[15,16] These studies compared the effects of exposure to smoke from VLNCs versus conventional cigarettes on adolescent mouse development. Analyzing brain tissue from dissected mice, they found that "even large reductions of nicotine yield in tobacco products do not spare the central cholinergic system," suggesting that VLNCs may still interfere with adolescent brain development in ways that are commonly thought to be associated with nicotine exposure.[15] Short- and long-term observations of adolescent mice also found that exposure to smoke from VLNCs impacted anxiety-like and novelty-seeking behaviors in ways that are similar to, though somewhat distinct from, regular cigarettes. For example, the mice exposed to VLNCs experienced increased long-term anxiety a few days after exposure, while those exposed to regular cigarettes experienced increased short-term anxiety by the end of exposure.[16]

Product evaluation studies do not directly measure health effects, but can provide estimates of exposure to smoking-related toxicants. Two studies used smoking machines to examine SPECTRUM research cigarettes and found that, in general, measured levels of a wide range of smoke constituents (other than nicotine) were similar to or slightly lower than the levels found in reference cigarettes.[36,37] One important exception, however, is that levels of tobacco-specific nitrosamines (NNN and NNK) may be correlated with nicotine content and thus may be lower in VLNCs. An Altria study[35] conducted on Philip Morris research VLNCs reached similar conclusions. It is well established that smoking machines do not accurately reflect human exposure.[93] Nonetheless, these studies suggest that the toxicity of VLNCs is likely to be similar to that of regular cigarettes—though NNN and NNK levels may be lower—*if they are smoked identically*. There were a few constituents that registered higher readings for VLNCs, which may suggest need for more research on those specific constituents.

The majority of health effects studies identified were human experimental studies (n = 15), and all but one of these studies reported the results of randomized control trials. The duration of these studies varied widely, from very short term to a year, and the trial protocols varied in both design and endpoints. Thus, this body of literature is summarized here at a high level of generality.

Human studies can provide better evidence than animal studies or product evaluation studies on the health effects of VLNCs *as they are actually used* by consumers, but the degree to which experimental conditions accurately mimic real life depends on the specific study. One global limitation noted by many authors was the high level of noncompliance (using non-study cigarettes) among current smokers assigned to use VLNCs (from 12% up to 78%),[20,67,70,71] which is at

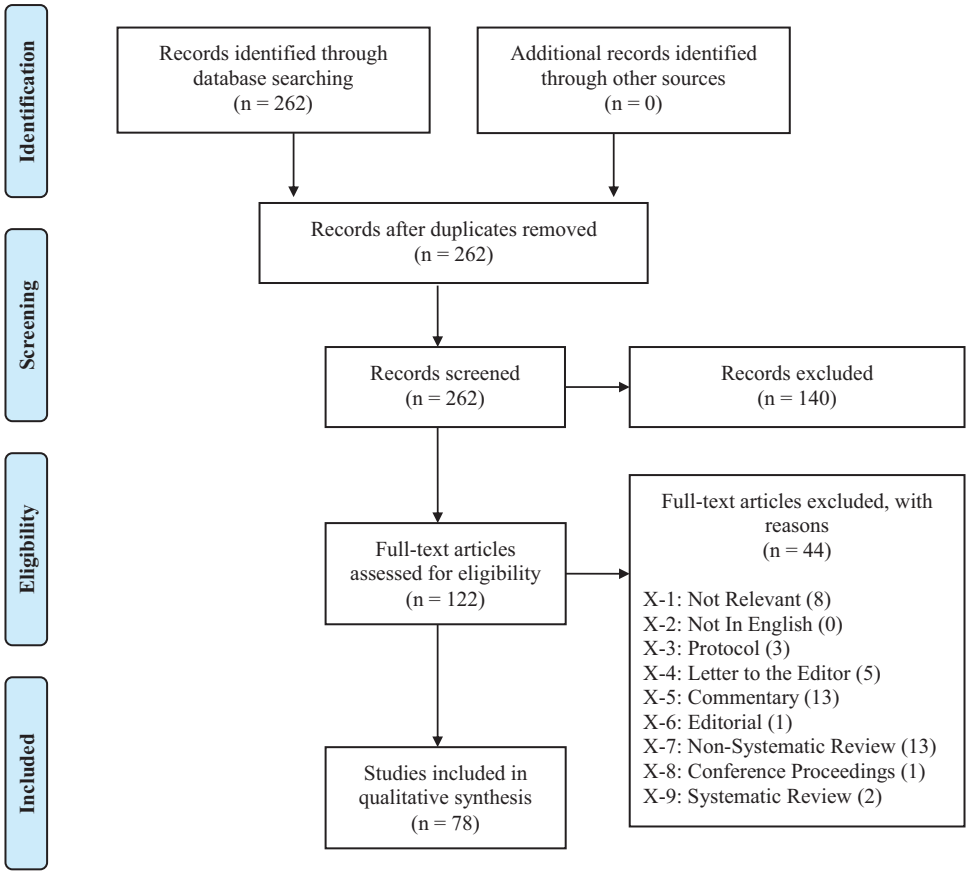

Figure 2. Flow diagram of included studies (n = 78).

least in part a function of the easy availability of conventional cigarettes in the current environment.

In general, the human studies found that among participants randomized to VLNC conditions, biomarkers of exposure to a range of smoking-related toxicants (CO, PAHs, TSNAs, VOCs) were lower than the levels found among those using conventional cigarettes—apparently due to a reduction in cigarettes consumed per day.[20–22] However, exposure levels were in some cases higher among those smoking "moderate nicotine content" cigarettes, suggesting that compensation may occur when nicotine levels are only somewhat reduced, but not when nicotine levels are reduced more substantially.[23–25] Studies by Hatsukami and colleagues have shown that providing access to NRT or other noncombustible nicotine products alongside VLNCs reduces levels of smoking and toxicant exposure even further.[21,26] These investigators also conducted a large (n = 1250) 20-week trial that directly compared an immediate shift to VLNCs against a gradual reduction in nicotine levels.[24] It concluded that "[a]mong smokers, immediate reduction of nicotine in cigarettes led to significantly greater decreases in biomarkers of smoke exposure across time compared with gradual reduction or a control group, with no significant differences between gradual reduction and control."[24]

Despite the reduction in smoking-related biomarkers of harm, other studies noted that moving current smokers to VLNCs could negatively impact cognitive function and memory[17–19] and could potentially prompt weight gain.[29] These studies suggest the possibility of harmful unintended effects if current smokers do not have access to other, less harmful sources of nicotine when a nicotine reduction product standard takes effect.

Dependence Potential, Withdrawal, and Subjective Effects

The key goal of a nicotine reduction product standard would be to minimize the abuse liability of cigarettes, in order to reduce current use and prevent uptake of the products. Both laboratory animal (n = 5) and human (n = 38) studies have examined the dependence potential of VLNCs and, relatedly, the potential withdrawal (and related effects) of transitioning from conventional cigarettes to VLNCs.

Although nicotine reinforcement thresholds cannot be easily translated from laboratory animals to humans, studies in both rats and mice suggest that "adolescent [animals] are less sensitive than adults to the primary reinforcing effects of nicotine."[38,39] This suggests that a nicotine level that is low enough to prompt adults to quit using cigarettes will also likely be sufficient to prevent youth dependence (this finding, however, conflicts with some previous studies not included in this review[94,95]). Other animal studies have sought to identify individual characteristics that might impact nicotine reinforcement thresholds. These studies suggest that there are few differences by sex,[40] but that "fast metabolizers of nicotine" are a potentially vulnerable group that should be taken into account when setting a maximum nicotine level.[41]

Human studies of dependence and withdrawal have been primarily (though not exclusively) in the form of randomized controlled trials (RCTs), again varying widely in terms of duration, products

Table 1. Outcomes Measured in Included Studies (*N* = 78)

Risk assessment component	Topic	Number of studies[a]	Outcomes measured
Effects assessment	Health effects	*N* = 20	*Animal studies* *Neurological effects: nAChRs ([3H]Cytisine binding)[15]; CHT ([3H]HC-3 binding)[15]; ChAT activity[15]; AChE activity[15] *Anxiety[16] *Body mass index[16] *Locomotor activity[16] *Human studies* *Cognitive measures: Conners' Continuous Performance Test II (CPT II)[17]; Cambridge Neuropsychological Test Automated Battery (CANTAB)[17]; Cognitive Failures Questionnaire (CFQ)[18]; motor functioning[17]; rapid visual information processing[17]; delayed matching to sample[17]; simple reaction time[17]; verbal n-back task[19] *Biomarkers of exposure: carbon monoxide[20–27]; polycyclic aromatic hydrocarbon (PAH) biomarkers[20,23–25,27,28]; 4-(methylnitrosamino)-1-(3) pyridyl-1-butanol (NNAL), 4-(methylnitrosamino)-1-(3)pyridyl-1-butanone (NNK), or N′-nitrosonornicotine (NNN)[20–22,24–26]; acrolein biomarker 3-HPMA[24]; acrylonitrile biomarker CEMA[24]; benzene biomarker SPMA[24]; propylene oxide biomarker 2-HPMA[24]; crotonaldehyde biomarker HMPMA[24]; 8-epi PGF2α[24]; prostaglandin E2[24] *Weight gain[29] *Center for Epidemiologic Studies Depression Scale (CES-D)[24,30] *Heart rate[31] *Blood pressure[31] *White blood cell count[24] *C-reactive protein[24] *Adverse events[24,32–34] *Product testing* *Total particulate matter and oxides of nitrogen[35] *Nicotine[35–37] *2-nitropropane (nitro compound)[35] *Tobacco specific nitrosamines (TSNAs)[35–37] *Metals[35] *Volatiles (water, hydrogen cyanide)[35] *Carbon monoxide[35,36] and inorganic compounds[37] *Aromatic amines, polyaromatic hydrocarbons (PAHs), and phenols[35–37] *Carbonyls and aldehydes[35,36] *Cytotoxicity[35] *Salmonella mutagenicity[35] *Tar[36] *Menthol[37] *Alkaloids[37] *Ammonia[37]
	Dependence potential	*N* = 43	*Animal studies* *Nicotine self-administration[38–43] *Human studies* *Modified Cigarette Evaluation Questionnaire (mCEQ)[26,34,44–52] *Cigarette Acceptance Questionnaire[20] *Modified Cigarette Liking Scale[49] *Cigarette Effects Scale[53] *Minnesota Tobacco Withdrawal Scale (MTWS)[20,21,26,31,32,45–47,50,53–57] *Wisconsin Inventory of Smoking Dependence Motives[24,30,32,57] *Questionnaire of Smoking Urges-brief scale (QSU-brief)[23,30,31,45–47,50,53,54,56,57] *Shiffman-Jarvik Withdrawal Scale[58,59] *Fagerström Test for Nicotine Dependence[19–21,23,24,26,27,30,32,44,45,49,54,55,57–62] *Modified Fagerström Tolerance Questionnaire (mFTQ)[52] *Hooked on Nicotine Checklist[49] *Penn State Cigarette Dependence Index (PSCDI)[49] *Glover Nilsson Smoking Behavioural Questionnaire (GN-SBQ)[34] *Autonomy Over Tobacco Scale (AUTOS)[34] *Smoking lapse analog task[31] *Mood and Physical Symptoms Scale[63]

Table 1. Continued

Risk assessment component	Topic	Number of studies[a]	Outcomes measured
			*Time to first cigarette[34] *Withdrawal symptoms[49,64] *Subjective effects (satisfaction, psychological reward)[25,51,61] *Nicotine metabolite ratio[27,58,59] *Plasma or urine cotinine or nicotine[20,24–27,57,65,66] *Total nicotine equivalents (TNEs)[21,22,24,26,44,48,55,57,64]
Exposure assessment	Patterns of use	*N* = 36	*Cigarettes per day[20,22,27,32,44,54,64,67,68] *Abstinence: 7-day point-prevalence abstinence[20,21,69]; continuous abstinence (various time-points)[21]; 24-hour quit attempts[22] *Measurement of noncompliance or attrition[67,70–74]
	Topography	*N* = 9	*Count: total number of puffs[23,25,46,54,56,75,76]; number of puffs per cigarette[75] *Inter-puff interval[25,46,56,75] *Volume: total session volume[25,44,53,54,56,75]; mean puff volume[25,46,54,56,75,76] *Mean puff duration[25,46,56,75,76] *Max or peak puff velocity[25,46,75]
Risk characterization	Modeling	*N* = 2	*Projected prevalence of cigarette smoking[77,78] *Projected prevalence of dual products use[77] *Tobacco-related deaths[77]
External factors	Other nicotine or tobacco product use	*N* = 2	*Past 30-day e-cigarette use[79] *"Any uptake" of alternative tobacco/nicotine product use[22]
	Other substance use	*N* = 4	*Alcohol: average number of weekly standard alcoholic drinks[80]; binge drinking of alcohol[80]; daily alcohol consumption[30] *Cannabis: past 30-day cannabis use[30,50,54]; daily cannabis use[30]
	Perceptions and pricing	*N* = 13	*Opinion about FDA's potential nicotine reduction[81–85] *Perceived health risks[61,86–91] *Future smoking intention with regulation[86,87,92] *Cigarette purchase task[45–47,50,60,76,79,92]

[a]Number of studies totals more than 78 because multiple studies are relevant to more than one section of the review.

tested, and subject populations. Studies range from short-term consumer perception trials, with exposure lasting a matter of hours, to experiments that followed participants for 6 months or more.

These varied studies are consistent in finding that VLNCs (usually 0.4 mg/g nicotine SPECTRUM research cigarettes) have far lower abuse liability compared to conventional cigarettes, measured primarily by the Cigarette Evaluation Scale. Although these studies were generally unable to use minors as subjects, they mirrored the animal studies in finding that VLNCs "may reduce smoking reinforcement more quickly in young adults" compared to older adults.[44] Likewise, they also confirmed the need to take high nicotine metabolizers into account when setting a nicotine product standard.[58]

The reduced dependence potential of VLNCs did not appear to be moderated by opioid dependence, affective disorders, or economic disadvantage,[45,46] or by cannabis use[54] or depressive symptoms.[30] There were conflicting results, however, regarding the impact of dependence severity at baseline.[27,47,55] Thus, the more cautious approach may be to view highly dependent current smokers as an additional vulnerable population to consider when setting a nicotine reduction product standard.

Despite the reduced dependence potential of VLNCs, a number of studies found that few subjects quit smoking entirely while assigned to use VLNCs (though many reduced the number of cigarettes smoked per day, as discussed below), and most subjects returned to pre-study levels of conventional cigarette use at the end of their trial period.[20,32,48] The failure of VLNCs to extinguish nicotine dependence could be the result of non-compliance with study protocols—as noncompliance was consistently listed as a limitation in these studies—but this is not clear.[22,72] It could also be due to the fact that VLNCs, despite their low levels of nicotine, appear to be effective in alleviating withdrawal. This suggests that "smoking-induced relief of craving and withdrawal reflects primarily non-nicotine effects,"[58] thus making VLNCs a partial substitute for conventional cigarettes, resulting in continued use.[60]

Though VLNCs appear to alleviate withdrawal, they are subjectively disliked by current smokers,[44] and an immediate shift to VLNCs may be associated with other negative effects connected to nicotine addiction including "increased anger/irritability/frustration."[55,64] Though these symptoms may be short-lived, they can be minimized by combining the use of VLNCs and NRT.[24]

Exposure Assessment

The effects assessment summarized above suggests that the potential of VLNCs to minimize the harm of smoking is largely dependent on reduced exposure to cigarettes, including decreased initiation and increased cessation. In this review, there were no human studies that examined initiation of smoking among youth. As VLNCs are not currently available commercially and it is unethical to conduct experiments on smoking initiation behaviors, we did not expect any such studies to have been published. Instead, we have summarized the studies examining the impact of VLNCs on cigarette consumption, smoking cessation, and smoking topography.

Patterns of Use: Cigarettes Per Day

There were 17 analyses from 12 studies measuring change in cigarettes per day (CPD) using VLNCs, all of which were RCTs. Studies ranged in length from 35 days[25] to 2 years,[20,27,68] but most studies examined behavior change over 6 weeks. Studies also varied in

whether the smokers included in the study were interested in quitting and whether nicotine reduction was gradual or immediate.

Some studies found that among current smokers interested in quitting or in using VLNCs, smoking quantity, measured by CPD, was lower among those using VLNCs compared to regular cigarettes.[25,61] Other studies found no difference in CPD between the groups.[23,28] One study by Hatsukami comparing the impact of use of VLNCs and nicotine patches over a 6-week period found that the VLNC plus patch group smoked the fewest assigned CPD.[21]

All but two studies[22,49] examining smokers not interested in quitting found lower consumption of CPD among VLNC smokers compared with regular cigarettes.[20,22,24,27,32–34,44,64,65,68] This relationship was modified by menthol smoking status. A 2-year, two-arm unblinded RCT of VLNC use (gradual tapering of nicotine content over time) (n = 103) found that the VLNC group had a significantly greater drop in CPD compared with the control group at 6 months and at 2 years; however, when menthol smokers were excluded from the analysis, there was no longer a difference between the groups.[20] Studies demonstrated a greater reduction in CPD over time among smokers experiencing an immediate reduction in nicotine compared with those experiencing a gradual reduction.[24,68] Smoking with non-study cigarettes was low, but higher in VLNC conditions.[23,32,33]

Patterns of Use: Smoking Cessation

Seven analyses from six studies measured smoking cessation outcomes. All were RCTs. Two studies found no difference in abstinence between regular cigarette groups and VLNC groups.[20,33] Another RCT comparing immediate versus gradual nicotine reduction found a higher mean number of cigarette-free days in the immediate reduction group compared to the gradual reduction group.[24]

There were mixed findings regarding the effectiveness of VLNCs compared to other quitting methods. The Hatsukami RCT previously mentioned comparing use of VLNCs (Xodus by 22nd Century Limited LLC), patches, and both found no significant differences across groups in terms of past-7-day abstinence from cigarettes at the 12, 24, and 36-week follow-up visits.[21] However, there was considerable effect modification by gender. Males using the patch reported the highest continuous abstinence at week 12 (20.6%) compared to those who received both products (6.1%) and only VLNCs (3.1%).[26] In contrast, among females, abstinence was highest among those receiving VLNCs (21.3%), followed by combination (14.0%) and patch (8.7%). Men had 2.32 times the odds of reporting abstinence using the patch compared with women, while they only had 0.5 times the odds of abstinence using VLNCs (same pattern was found at weeks 24 and 36).[26] An RCT comparing standard treatment to standard treatment plus VLNCs among smokers with a target quit date (TQD) found significantly higher CO-validated quit rates at week 4 post-TQD for the VLNC group (51% vs. 31%); after controlling for baseline differences in those who quit and those who did not, the association remained significant (OR = 2.38; 95% CI: 1.26–4.46).[63]

Smoking Topography

Six analyses from five studies measured puff topography in lab experiments. In general, VLNCs were smoked less intensely than regular cigarettes with some exceptions.[44,46] One RCT found no effect of nicotine dose on total puff volume, but a decrease in puff count among non-cannabis users of VLNCs (no decrease in cannabis users).[44,54] Other studies found higher puff volume[23,53,56] (including among schizophrenic smokers)[75] and puff count[56] with usual brand cigarette use compared with VLNC use.

External Factors

Other Tobacco Product Use

An important component that may impact exposure in the event of a reduced nicotine product standard includes the likelihood that smokers will switch to less harmful nicotine products. In addition, it is important to know whether smokers will switch to other combustible tobacco products (ie, not less harmful). Only three studies assessed use of other tobacco products.

One study simulated an environment comparing the current tobacco marketplace to one where smokers using VLNCs would have access to all other current products on the market or to only non-combustible products.[22] VLNC users who had access to all other products reported the highest rate of alternative product use, followed by those who had access only to non-combustibles, and then smokers of regular cigarettes with access to all current products. VLNC groups reported fewer combustible products used, and as combustible product use declined over the 8-week study, use of non-combustible products increased.[22] E-cigarettes were the most common alternative product reported, although cigar smoking increased over time among the VLNC group with access to all other products. Another study found that demand did not differ between e-cigarettes and VLNCs, but demand for regular cigarettes was higher compared to both products.[79] A study assessing noncompliance to study cigarettes in an RCT found that the most commonly used product among noncompliant smokers was e-cigarettes (0.8% of the study days), and among smokers not using e-cigarettes at baseline, new use of e-cigarettes was significantly more common among the VLNC group in the trial, especially among heavier smokers.[33]

Other Substance Use

There were only four studies measuring use of non-tobacco substances in conjunction with VLNCs. Studies suggest that there is no compensatory alcohol use,[30,80] and that VLNCs may actually be associated with reduced alcohol consumption.[80] No effect of VLNC use on cannabis use was found,[30,50,54] but cannabis has been found to be a moderator of the relationship between VLNC use and other outcomes.[54] For example, one study found decreases in positive affect and smoking urges among cannabis users (but not nonusers) when randomized to VLNCs.[54]

Perceptions

Because the key difference between conventional cigarettes and VLNCs is the nicotine content, perceptions about nicotine and what that means for the risks associated with VLNC use are critical factors to determine the success of these products as a policy option. There were five studies measuring support for a reduced nicotine product standard and seven studies examining perceived risks of VLNCs included in this review.

A nicotine reduction product standard has relatively high support among adults in the United States, with support measured at 46.7% in 2010[81] and 76.2% in 2011 (not a nationally representative sample).[82] Support is higher among nonsmokers compared with smokers,[81,82] and among non-white Americans compared with white Americans.[81–83] A study of policy stakeholders and smokers in New Zealand highlighted some of the concerns with feasibility of the policy, with many being concerned about VLNCs' effectiveness

if conventional cigarettes are still on the market and the potential tobacco industry response.[84]

Misperceptions about nicotine and about VLNCs may have an impact on behavioral intentions.[61,86] One 2016 study found that in the United States, about half (47.1%) of smokers misperceived VLNCs to be less carcinogenic than regular cigarettes, and 23.9% reported they would be less likely to quit smoking if nicotine content in cigarettes was regulated, an intention that was more common among smokers with cancer misperceptions.[86] Other studies found, however, that people queried about VLNCs were mostly correct about the risk of these products,[87–89] with greater misperceptions among foreign-born US residents,[90] older adults, racial/ethnic minorities, and those with less education.[89]

Price/Behavioral Economics

Eight analyses from five studies measured demand for VLNCs, mostly measured by cigarette purchase task lab experiments. These studies provide some evidence of the possible impact of pricing on VLNC use, and they also concurrently serve as a means of measuring dependence. Studies showed higher demand for regular cigarettes compared to VLNCs, particularly among more dependent smokers and those not motivated to quit.[45,46,60] However, there was a significant effect of cost, with increased cost of regular cigarettes (alongside a constant price of VLNCs) resulting in greater demand for VLNCs,[60,76] suggesting demand for VLNCs may increase as it becomes more difficult to obtain conventional cigarettes. A large double-blind RCT comparing usual brand cigarette with six different VLNC conditions found that reduced nicotine decreased the number of cigarettes people estimated they would smoke and increased the number of smokers who reported they would not smoke across a range of prices.[92]

An experimental study (no comparison group) of adult daily smokers with affective disorders, opioid dependence, and social disadvantage found that demand was higher for conventional cigarettes compared with VLNCs, but this was reversed when the cost (more required clicks on the computer) of the conventional cigarettes increased.[45] The effect was independent of dependence severity[47] and cannabis use.[50]

Risk Characterization

Modeling Studies

Modeling the impact of VLNCs over time accounts for factors related to both initiation and cessation of cigarettes as well as use of other tobacco products, enabling policymakers to predict how a reduced nicotine product standard may impact tobacco use at the population level. In this review, two simulation modeling studies were included, one in the United States,[77] and one in New Zealand.[78] The US-based study included roll-your-own tobacco, pipe tobacco, and non-premium cigars in addition to cigarettes in the proposed policy, and the New Zealand-based study included roll-your-own tobacco along with cigarettes. The New Zealand model also includes the effect of a 10% excise tax increase annually, and the combined policy simulation found that smoking would be reduced to 4.1% by 2025.[78]

The US study projected that in just 1 year, smoking prevalence with a reduced nicotine policy would be 16% lower, any tobacco use would be 7% lower, and an additional five million smokers would have quit.[77] By 2060, smoking prevalence would drop to 1.4% and any tobacco product use to 11.6% (82% and 17% lower than status quo, respectively). By 2016, an estimated 2.8 million tobacco-related deaths would be averted, increasing to 8.5 million by 2100. Though potentially instructive, this study relied heavily on expert elicitation for its inputs, whereas risk characterization in a risk assessment would typically incorporate the data collected in the previous phases of the assessment.

Discussion

This systematic literature review provides a high-level overview of the research that has been done on the impact of a potential FDA nicotine reduction regulation. The goal of this review was to identify the broad contours of this body of literature in order to identify gaps that must be filled to fully complete a risk characterization of VLNCs. This review did not seek to conduct a formal quality assessment of the included studies.

Effects Assessment

The majority of studies in this systematic review (n = 48) related to the effects assessment phase of a risk assessment and reviewed either the health effects or dependence potential of VLNCs. This review found few studies directly assessing the dose-related effects of VLNCs, but given the similarities of VLNCs to conventional cigarettes, the extensive body of literature examining the dose-dependent effects of conventional cigarettes can likely be used to fill this gap. The health effects studies, including both animal and human studies, generally found that the health harms of VLNCs are likely to be similar to (although potentially slightly less than) conventional cigarettes if consumed in a similar manner and quantity. However, the dramatically lower dependence potential of VLNCs suggests that a reduced quantity of usage is likely.[20–22] A policy that reduces nicotine levels immediately, rather than gradually, will reduce toxicant exposures faster.[24] A rapid reduction in nicotine, though, comes with potential side effects—including a negative impact on cognitive function and memory—which emphasizes the role for less harmful alternative nicotine products.[17–19] A recent review of the effects of VLNCs on behavioral and cognitive performance confirms these findings, reporting improved outcomes when VLNCs were used with nicotine replacement therapy.[96] Though there appears to be a considerable body of literature addressing this first phase of the risk assessment, the Tobacco Product Assessment Consortium framework could be used for a more fine-grained assessment of particular types of studies that might provide additional insights.[4]

Exposure Assessment

For the exposure assessment phase, numerous studies (n = 36) address how VLNCs might alter patterns of cigarette smoking. In this review, there was broad agreement that VLNC use was associated with a decline in cigarettes smoked per day, even among those not interested in quitting.[20,22,24,27,32–34,44,64,65,68] However, this effect may be moderated by menthol cigarettes, as two studies show a reduction CPD among menthol smokers, but not among non-menthol smokers.[20,32] Menthol smokers have been shown to have more difficulty quitting,[97] so this finding is somewhat inconsistent with the literature and should be further explored. It is possible that switching to cigarettes that are different in both nicotine content and flavor combined could have led to more dissatisfaction with the cigarettes, further reducing consumption.[48] In general, although VLNCs appear to reduce CPD, they do not lead to full cessation in most cases, in part because cigarettes with low nicotine levels appear to still be effective in alleviating nicotine withdrawal.[58] Continued use of the VLNCs

could also be related to the fact that the study cigarettes were free, and many studies did not allow use of alternative nicotine delivery systems (ANDS) and/or enrolled smokers not interested in quitting. Not including users of ANDS is also a limitation of the studies, as there is a high prevalence of non-combustible tobacco product use in the United States, and it is likely that smokers using VLNCs will have the option of using ANDS to quit smoking. The lack of complete cessation deserves further exploration, as even a low number of CPD may be associated with significant health risks.[98]

Though most studies focused generally on adults who currently smoke, there were nine studies that included vulnerable smokers, including those diagnosed with schizophrenia, mood or anxiety disorders, opioid use disorders, or other mental illness. For some individuals in these categories, there may be an unintended effect of actually increasing cigarettes smoked or compensatory smoking, at least initially.[49,53,75] However, VLNCs appear to mainly be beneficial for the vulnerable groups included in this review, which is consistent with previous reviews indicating that VLNCs may help alleviate mood disruption accompanying quitting.[99,100]

The TCA mandates that the FDA consider the likely impact on initiation, cessation, and relapse. Though a powerful effect on youth initiation can be logically predicted, there are few studies directly focused on this question (although there are ongoing unpublished studies among youth and young adults).[101,102] Where clinical studies may be unethical or impossible to conduct, animal studies can be used to further address this question. Likewise, both animal and human studies have identified populations (eg, fast nicotine metabolizers) that would be most vulnerable to the effects of any amount of nicotine remaining in cigarettes. Further studies could help ensure that thresholds are identified to ensure that such populations reduce their exposure (both through reduced initiation and increased cessation) in response to a nicotine product standard.

This body of literature suggests how a nicotine reduction rule might impact cessation, but there is relatively little research that examines how consumers might use VLNCs in the context of other tobacco/nicotine products. Our review found a limited number of trials (mostly led by Hatsukami) exploring the impact of the availability of alternative nicotine products, but more work is needed in this area. For example, given the prevalence of dual use of e-cigarettes and cigarettes, it is important to explore whether a nicotine product standard would promote complete transitions to e-cigarette use (or the use of other alternative nicotine products) or instead lead to prolonged dual use alongside VLNCs. Our review did not identify any studies directly assessing how VLNCs might impact relapse by former smokers.

External Factors

External factors have not yet been fully integrated into research designs. Furthermore, the studies in this sample fail to address possible tobacco industry responses to a nicotine product standard (eg, development of synthetic nicotine products that could evade regulation or promotion of other combustible products not covered by a nicotine reduction rule) or the potential scope of black market sales. The latter gap is particularly important, given that the TCA specifically instructs the FDA to consider any information it receives about the potential "creation of a significant demand for contraband," and the tobacco industry is likely to focus on this issue.[7] A recent article described strategies that FDA could use to minimize illicit trade when implementing a nicotine reduction product standard, but it was published after our search date so is not included in this review.[103]

Risk Characterization

There were only two modeling simulation studies found in the literature, and they both predict a positive population impact of a nicotine reduction policy.[77,78] Since VLNCs are not available commercially, more high-quality modeling studies are necessary to predict the overall impact of a reduced nicotine standard in conjunction with other tobacco control measures.

Limitations

This review has several limitations to note. First, only articles indexed in PubMed were included; however, we are confident that most studies relevant to this review were captured in the search. Second, we only included studies published after 2013 based on external expert opinion regarding the relevance of nicotine reduction studies following the provision of research cigarettes provided by the National Institute on Drug Abuse (SPECTRUM). Despite this, we were able to pick up where previous reviews left off,[10,11] thereby avoiding duplication of effort. Third, some studies in this review were limited by participant noncompliance or differential attrition,[20,67,73,74] and several studies reported on validation of measures to most accurately assess compliance in future studies.[20,67,71,74] Fourth, although an ultimate goal is to quantify risk of VLNCs, this initial paper was intended to provide an overview of the framework and the published literature, so future review of subsets of these data will be meta-analyzed where possible. Finally, because this is an overview and gap analysis, full characterization of studies' risk of bias was not assessed, but will be in future review of these studies.

Conclusion

A review in 2014 identified some key research gaps in the reduced nicotine content literature, including the impact of gradual versus immediate nicotine reduction, the effect of reduced nicotine products on vulnerable populations or youth, and the use of other tobacco products in conjunction with VLNCs.[10] This review shows that some of these gaps have been filled—for example, the comparison between immediate reduction and more gradual reductions has now been studied[24,68]—while others remain. Additionally, the continually evolving marketplace for nicotine products generates new needs for current research. In our view, however, given the overwhelming amount of harm caused by combusted tobacco products and the substantial and rapidly growing body of literature on nicotine reduction, the remaining research gaps should not prevent the FDA from moving forward with the rulemaking process.

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Declaration of Interests

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