



Original Investigation

Dependence on Tobacco and Nicotine Products: A Case for Product-Specific Assessment

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Received December 4, 2011; accepted January 9, 2012

Abstract

The International Classification of Diseases and the Diagnostic and Statistical Manual for diagnosing tobacco/nicotine dependence emphasize the dependence-producing drug nicotine. These diagnostic tools have been challenged on grounds of poor predictive validity, and they do not differentiate across various forms of nicotine-containing products. In fact, nicotine-containing products (e.g., tobacco cigarettes, smokeless tobacco [ST], waterpipe, electronic cigarettes [ECIGs], and nicotine replacement [NR] products) have very different characteristics both in terms of sensory and behavioral involvement and also in pharmacokinetic and pharmacodynamic effects. For example, a cigarette and a nicotine patch are very different on almost every one of these dimensions. When ability to stop using a nicotine/tobacco product is used as a criterion for dependence, success rates vary considerably across products: Tobacco cigarette cessation is more difficult than ST cessation that in turn is more difficult than NR product cessation. Based on these results, we hypothesize that there is a continuum of dependence as much as there is a continuum of harm, with tobacco cigarettes and NR products on opposite ends of both continua and other products (waterpipe and ECIGs) somewhere in between. In order to capture more precisely the dependence produced by both nicotine and its administration forms, product-specific instruments may be required. The pros and cons of this approach are discussed.

Introduction

Drug dependence is a behavioral disorder that involves cellular adaptation to chronic drug exposure (Watkins, Koob, & Markou, 2000). In humans, observing this cellular adaptation is challenging at best and efforts to do so involve sophisticated imaging techniques (Brody, 2006). For diagnostic purposes, these imaging techniques are prohibitively expensive. For some dependence-producing drugs, like opioids (e.g., heroin, morphine) and alcohol, the effects of the cellular adaptation that accompanies chronic exposure can be revealed when a period of drug

abstinence produces a robust and observable “spontaneous” withdrawal syndrome (Edwards, 2006). Cellular adaptation can also be revealed, at least for opioids, when administration of a mu-opioid receptor blocker (i.e., an antagonist like naloxone) is administered and a robust “antagonist-precipitated” withdrawal syndrome is observed (Madhavan, He, Stuber, Bonci, & Whistler, 2010). While not definitive, spontaneous and antagonist-precipitated withdrawal contribute to a diagnosis of opioid or alcohol dependence (e.g., American Psychiatric Association [APA], 1994; Fudala, Berkow, Fralich, & Johnson, 1991). With nicotine, primarily self-administered via tobacco products like cigarettes, spontaneous withdrawal is often mild and not observable (Buchhalter, Acosta, Evans, Breland, & Eissenberg, 2005; Shiffman & Jarvik, 1976), and antagonist-precipitated withdrawal has been observed in nonhuman animals (Malin et al., 1997) but not in humans (Eissenberg, Griffiths, & Stitzer, 1996). Thus, assessing nicotine dependence requires other techniques, including self-report measures.

Tobacco dependence is a diagnosis under the World Health Organization's (1993) International Classifications of Diseases and Injuries (ICD), while the APA's (1994) Diagnostic and Statistical Manual IV (*DSM-IV*) refers to nicotine dependence. ICD and *DSM-IV* list criteria that must be met in order for an individual to receive a diagnosis of tobacco/nicotine dependence, and these criteria involve self-report measures of tolerance, loss of control, and other behaviors such as relapse during a quit attempt and presence of withdrawal symptoms. However, ICD and *DSM-IV* criteria have been challenged on grounds of poor predictive validity (e.g., Baker, Breslau, Covey, & Shiffman, 2011; DiFranza & Ursprung, 2010), and in any case, many other psychometrically sound and validated self-report measures exist for assessing nicotine dependence in cigarette smokers including the Cigarette Dependence Scale (Etter, 2008), Nicotine Dependence Syndrome Scale (Shiffman, Waters, & Hickcox, 2004), Hooked on Nicotine Checklist (Wellman et al., 2006), and Wisconsin Inventory of Smoking Dependence Motives (Piper et al., 2008). One self-report measure that is used very commonly is the “Fagerström Test for Nicotine Dependence” (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), recently

doi:10.1093/ntr/nts007

Advance Access published on March 29, 2012

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renamed the “Fagerström Test for Cigarette Dependence” (FTCD; Fagerström, 2011). The principal difference between diagnostic tools such as the ICD and *DSM-IV* and the FTCD is that ICD and *DSM-IV* use similar criteria for all drugs of dependence, while the FTCD uses criteria that are specific to the substance (nicotine) and the product used (cigarette). In this paper, we begin by noting that the types of products used for nicotine self-administration are numerous and increasing and that use of these products involves an array of product-specific salient behaviors and stimuli. We also present evidence that dependence level may be a function of product and that behavior and stimuli that accompany nicotine self-administration are critical in understanding dependence. We then argue that in addition to clarity, brevity, and sound psychometrics (e.g., Baker et al., 2011), accurate assessment of nicotine/tobacco dependence will require product-specific measures that take into account nicotine pharmacology, product characteristics, and the accompanying behaviors and stimuli. Thus, with each new type of product used for nicotine self-administration, a new measure may be required.

New Tobacco Products

Today most nicotine dependence scales measure dependence in cigarette smokers with some attempt to also measure dependence in smokeless tobacco (ST) users (e.g., Thomas, Ebbert, Patten, Bronars, & Schroeder, 2006). However, other nicotine/tobacco products are now becoming popular worldwide, including waterpipe (hookah, shisha, narghile), dissolvable ST products, electronic cigarettes (ECIGs), and nicotine replacement (NR) products. As described below, these products involve unique behaviors and stimuli, and thus, using traditional measures for cigarettes with a straightforward adoption to other products may not be optimal.

Waterpipe

A waterpipe has a head, body, bowl, and hose with mouthpiece. The tobacco in the head is sweetened, is available in virtually any flavor (e.g., strawberry, cappuccino, piña colada), and is very moist: It does not burn in a self-sustaining manner. Thus, lit charcoal is placed atop the tobacco-filled head. Users inhale through the mouthpiece and hose, drawing air over the charcoal. The heated air, that now also contains charcoal combustion products, passes through the tobacco, and the mainstream smoke aerosol is produced. Smoke passes through the body and the water in the bowl and is carried through the hose to the user (e.g., Martinasek, McDermott, & Martini, 2011). A single waterpipe tobacco-smoking episode lasts 30–60 min and exposes users to about 1.7 times the nicotine as a single cigarette (as well as 4 times the carbon monoxide and 48 times the smoke; Eissenberg & Shihadeh, 2009). That waterpipe tobacco smoking is now a global phenomenon is apparent from data from a variety of countries including Canada (Roskin & Aveyard, 2009), Denmark (Jensen, Cortes, Engholm, Kremers, & Gislum, 2010), Estonia (Pärna, Usin, & Ringmets, 2008), Germany (Bundeszentrale für gesundheitliche Aufklärung, 2007), Lebanon (Saade, Warren, Jones, & Mokdad, 2009), Jordan (Azab et al., 2010), South Africa (Combrink et al., 2010), Syria (Almerie et al., 2008), and the United States (Barnett, Curbow, Weitz, Johnson, & Smith-Simone, 2009; Primack, Fertman, Rice, Adachi-Mejia, & Fine, 2010; Sterling & Mermelstein, 2011; Sutfin et al., 2011). Waterpipe tobacco smoking is associated with a variety of cues that differ from

those of cigarette smoking, including a sweet smelling smoke that comes in many different flavors, an intricate preparation ritual, a sedentary rather than active smoking experience, and frequently group rather than individual use.

The notion that waterpipe tobacco smoking supports dependence has been discussed previously (e.g., Cobb, Shihadeh, Weaver, & Eissenberg, 2011; Maziak, Eissenberg, & Ward, 2005; Maziak, Ward, & Eissenberg, 2004), and here we note four key dependence indicators. First, the fact that waterpipe smoke delivers the dependence-producing drug nicotine (e.g., Cobb et al., 2011; Shafagoj, Mohammed, & Hadidi, 2002) indicates the potential for waterpipe use to support physical dependence. Second, a hallmark of dependence is unsuccessful quit attempts, and these occur (Ward et al., 2005). Third, surveys indicate that at least some users endorse items indicating that they are “hooked on waterpipe” (Smith-Simone, Maziak, Ward, & Eissenberg, 2008). Fourth, abstinent daily waterpipe users report withdrawal symptoms that are suppressed by waterpipe use (e.g., Rastam et al., 2011). Thus, available evidence from clinical studies, surveys, and qualitative interviews all support the idea that tobacco smoking using a waterpipe supports tobacco/nicotine dependence. However, to date, there has been only one published waterpipe dependence measure (Salameh, Waked, & Aoun, 2008).

Smokeless Tobacco

ST is orally consumed and not burned. A variety of types of ST are consumed throughout the world. In the United States and Nordic countries, the principal types of ST are snus (moist ground tobacco) and chewing tobacco (cut tobacco leaves). Use of ST is less social than smoking waterpipe and cigarettes, and its nicotine absorption kinetics differ from those of cigarettes, although the total amount of nicotine consumed approximates that seen in cigarette smokers (Holm, Jarvis, Russell, & Feryerabend, 1992). ST is relatively discrete and can be used where smoking is banned. The sensory stimulation and cues that accompany ST use differ from those associated with cigarette smoking. The main characteristics are: a smell from the product when the container is opened and when used, a taste is perceived and some irritation on the mucosa where it is placed and a bit of pressure under the lip (for snus).

More recently, dissolvable ST products (orbs, films and sticks) have been introduced in the United States. Their impact on the market has been relatively small so far. Generally, they seem to give rise to lower blood nicotine concentrations (Gray, Breland, Weaver, & Eissenberg, 2008; Kotlyar et al., 2007) than the traditional ST products—snus and chewing tobacco. The film is tucked to, for example, the palate and will dissolve by itself, while the stick and the orb (tablet) can be manipulated and sucked. As indicated above, there are few measures available for assessing nicotine/tobacco dependence in ST users (e.g., Boyle, Jensen, Hatsukami, & Severson, 1995; Ebbert, Patten, & Schroeder, 2006; Ferketich, Wee, Shultz, & Wewers, 2007; Thomas, et al. 2006), although there is evidence for the dependence potential of this form of tobacco use (Difranza, Sweet, Savageau, & Ursprung, 2011; Post, Gilljam, Rosendahl, Bremberg, & Galanti, 2010). None of the available measures have been applied to and validated with users of dissolvable tobacco products.

Electronic Cigarettes

Relative to cigarettes, waterpipe, and ST, ECIGs are very new nicotine self-administration products. An ECIG consists of a

Dependence on tobacco and nicotine products

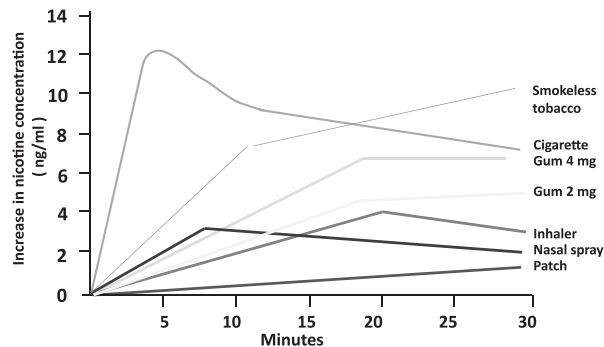
battery-powered heater and a supply of nicotine-containing liquid that is often flavored and uses propylene glycol and/or vegetable glycerin as its base (e.g., Cobb, Weaver, & Eissenberg, 2010). When activated, the heater vaporizes some of the liquid, which is then inhaled by the user. ECIG components are often packaged into a cylinder that approximates the look and feel of a cigarette, although different designs are becoming more common (Foulds, Veldheer, & Berg, 2011). Initial results suggested that ECIGs delivered very little nicotine (e.g., Bullen et al., 2010; Vansickel, Cobb, Weaver, & Eissenberg, 2010), though more recent studies suggest that there are conditions under which these products can deliver nicotine levels that approximate those of a cigarette (e.g., Etter & Bullen, 2011; Vansickel & Eissenberg, 2012). Some of the stimuli associated with ECIG use mimic those of a tobacco cigarette (e.g., the look and feel of the vapor; the hand-to-mouth movement that accompanies vapor inhalation), although others do not (i.e., taste and smell: The liquid is available in hundreds of flavors that include fruits, desserts, spices, etc.). A growing literature suggests that some cigarette smokers have begun using ECIGs exclusively (i.e., are no longer smoking tobacco cigarettes) and continue to do so for months (Etter & Bullen, 2011). These reports, coupled with data suggesting substantial nicotine delivery to the user (Vansickel & Eissenberg, 2012), suggest that ECIGs may produce/maintain tobacco/nicotine dependence. No measure for assessing tobacco/nicotine dependence in ECIG users has been published.

NR Products

Although these products are derived from tobacco—the nicotine comes from tobacco—they are so far regarded as medicines when accompanied by health claims. They are usually not referred to as tobacco products but clean or pure nicotine products and used for the most part as a treatment for tobacco dependence. They differ in various ways from tobacco products. The motivation to use them is mainly to make it easier to stop tobacco altogether. Thus, they are usually used for a short period of time, weeks to months. Their nicotine absorption characteristics are different to most other tobacco products (Benowitz, 1990). The rapid uptake, as from cigarettes and ST, is not seen (with the possible exception for nasal and oral sprays), and the sensory impact is usually smaller (Figure 1). For example, with a patch, there is hardly any sensory impact at all. With the oral products that are most used, gum and lozenge, there is some behavior involved, sucking and chewing. The products comes in several flavors but are nevertheless usually not rated as pleasant because of the irritating effect of nicotine in the mouth and upper part of the throat (Schneider et al., 2005). There are no social habits around these products that are usually used in isolation, and discreetness is a positive asset for these products. Indicators of nicotine dependence have been observed in NR product users (e.g., Hatsukami, McBride, Pirie, Hellerstedt, & Lando, 1991; see also Hatsukami, Huber, Callies, & Skoog, 1993), but no scale to assess this dependence has been developed.

Summary

Table 1 summarizes characteristics of the various tobacco/nicotine products discussed here. As the table makes clear, cigarettes are not the only method of nicotine self-administration. As water-pipe, ST, ECIGs, and other nongarette products become more popular, addressing the potential for them to support dependence becomes more important. We next consider the extent to which tobacco/nicotine dependence is a function of the product used.



Source: Balfour DJ & Fagerström KO. *Pharmacol Ther* 1996 72:51-81.

Figure 1. Plasma nicotine concentrations for some nicotine and tobacco products.

Is Dependence a Function of Product?

Repeated use of tobacco products, particularly tobacco cigarettes, appears to be related to nicotine as well as nonnicotine factors. Consumption of nicotine is not associated with euphoria and positive effects comparable to drugs like cocaine and amphetamine (Goldberg, Spealman, Risner, & Henningfield, 1983) and in its pure form (NR), it is a weak reinforcer in humans (Hughes, Rose, & Callas, 2000; Perkins, Gerlach, Broge, Fonte, & Wilson, 2001). Abstinent smokers seem to prefer a much reduced nicotine content cigarette over nicotine containing products like gum, and the reduced nicotine cigarette reduces craving (Barrett, 2010; Buchhalter et al., 2005; Donny, Houtsmuller, & Stitzer, 2007) and alters brain nicotinic acetylcholine receptor occupancy (Brody et al., 2009). Although nonhuman animals self-administer nicotine, its reinforcing effects are relatively weak and, interestingly, become stronger when the drug is presented in the presence of nicotine-paired environmental cues (Caggiula et al., 2002).

The strong dependence potential of tobacco products despite the above observations may be a function of the rapidity with which tobacco-delivered nicotine reaches the brain (Figure 1) and the behavioral and sensory stimulation that accompany cigarette smoking and may also reflect the influence of other nonnicotine substances in tobacco that contribute to dependence (Talhout, Opperhuizen, & van Amsterdam, 2007).

In order to examine the dependence levels produced by chronic use of different tobacco products in this section, we operationalized dependence as “difficulty quitting” using the Cochrane system for estimating cessation success. In the Cochrane (2011) reviews, only methodologically sound studies are accepted and the follow-up period must be at least 6 months. It was decided to use the large body of well-conducted studies with pharmaceutical products since they are relatively similar in design across studies. The intention here was not to estimate the effect of the treatment but rather its placebo to determine how difficult it is to stop using a certain form of tobacco/nicotine product. Therefore, the success rate in the placebo group is used as indicators for difficulty abstaining. Table 2 shows that cigarette smokers, independent of treatment, show a success rate of roughly 10% with little variation (range 9.8–11.2). Those seeking to stop ST use have roughly more than double the success rate of cigarette smokers (range 19.1–33.0).

Table 1. Characteristics of Different Tobacco and Nicotine Products

Product	Cigarettes	Waterpipe	Smokeless	E-cigarettes	Nicotine replacement
Mode of use	Lighted, hand-to-mouth inhalations, exhalations through mouth or nose.	Heated with charcoal, hand-to-mouth inhalations, exhalations through mouth or nose.	In the mouth. Chewed (chewing tobacco), placed under upper lip (moist tobacco), sucked (dissolvables).	Electronic heating of liquid to form a vapor; hand-to-mouth inhalations, exhalations through mouth or nose.	Patches applied on skin. Sprays by mouth or nose. Inhalator inhaled and all others chewed, sucked or automatically dissolved in the mouth.
Sensory stimulation	Very rich. Visual smoke, taste, smell, impact on throat and airways.	Very rich. Visual smoke, taste, smell; elaborate preparation rituals.	Taste and smell. Some burning on the mucosa where pinch or pouch placed.	Vapor is much lighter than cigarette or waterpipe smoke but many possible flavors.	Product dependent. Patch nothing. Oral and nose products, taste, smell and irritation on mucosa.
Duration of use	~5–7 min	30–60 min	~20–40 min	Uncertain; anecdotal reports suggest near continuous use throughout a day.	Patch 24 hr. Oral products ~20–30 min. Inhalator ad lib puffing.
Absorption of nicotine	From lung tissue. Arterial boli.	Has not been addressed empirically.	Across the oral mucosa. No arterial boli.	Has not been addressed empirically.	Across the skin or oral mucosa. No arterial boli.
Social elements	Often together with others bonding. Can be a cause for a break.	Often used in small groups.	Often not social. Used discrete.	Has not been addressed empirically.	Seldom used socially.

In the study (Tonnesen & Mikkelsen, 2012), where 69 long-term users of pure nicotine mostly in the form of gum, in average seven years, a success rate of 36% was observed.

Those who become long-term users of nicotine replacement therapy (NRT) are recognized as heavy dependent smokers (Hajek, Jackson, & Belcher, 1988), which also seemed to be true in this study. Their cigarette consumption before quitting was

24.5 per day and their recalled FTCD score from when they were smoking was a high 6.7. It can be hypothesized that this type of smoker would have had no better success rate in stopping than the 10% seen normally but when coming off long-term NRT, it was 36%. The 36% was obtained from a 1-year follow-up. Several of the smokeless studies reported success rates from 6 months. It is of interest to note that the authors excluded long-term patch users since it would have been unlikely to see a difference between active and placebo treatment due to the ease by which they normally can stop. Moreover, it is much more infrequent to observe long-term patch use (Shiffman, Hughes, Pillitteri, & Burton, 2003). It seems as a patch is not very likely to be able to support a compulsive use pattern due to its little behavioral involvement and or pharmacokinetic nicotine uptake pattern.

Table 2. Success in Stopping Using Different Tobacco/Nicotine Products in Percent When Exposed to Different Placebo Products

Cigarette cessation		Success rate (%)
(Cochrane, 2011)	Nicotine gum	11.2
	Nicotine patch	9.8
	Varenicline	10.0
	Bupropion	10.2
SLT Cessation (Cochrane, 2011)	Nicotine gum	26.6
	Nicotine patch	25.5
	Nicotine lozenge	21.1
	Varenicline	33.0
	Bupropion	19.1
Cessation of long-term use of nicotine replacement therapy (Tonnesen & Mikkelsen, 2011)	Varenicline	36.2

The data in Table 2 lead us to conclude that quitting cigarette smoking is more difficult than quitting ST (Fagerström, Gilljam, Metcalfe, Tonstad, & Messig, 2010) and, although there is only one study from the NR category, that quitting these products may be easiest (Tonnesen & Mikkelsen, 2012). Of course, these data might be explained by a self-selection bias (e.g., cigarette users and ST users could be from different populations). However, another plausible explanation is that the differing nonnicotinic factors and pharmacokinetics of nicotine across the different categories are relevant. We propose that dependence—the robust phenomenon that causes withdrawal, continued use despite adverse health consequences, difficulty quitting, etc.—differs across tobacco/nicotine products. As it looks from the data in Table 2, the cigarette may be, in addition to the most harmful

product, the most dependence-producing product. Indeed, just as there is likely a profound difference in harmfulness between the products—a continuum of risk (Zeller & Hatsukami, et al., 2009)—there might also be a continuum of dependence. The cigarette seems to be in the high dependence end of this continuum, while NR products, and particularly the patch, seemed to be positioned in the low end of the dependence continuum. ST appears to have an intermediate position on the dependence continuum. Where other tobacco products are positioned on both of these continua is an empirical question deserving of immediate research.

Can We Assess Tobacco/Nicotine Dependence More Precisely With Product Specific Instruments?

There are fundamental differences between administration forms of the same substance. For example, the cigarette that delivers nicotine in association with a rich behavior ritual and with rich sensory impact differs considerably from the nicotine patch that delivers nicotine almost without behavior involvement except for applying it once a day and with little or no sensory impact. Apart from the differences in behavior and sensory characteristics, there are also profound differences in pharmacokinetic parameters. While the patch in principle sustains an even concentration of nicotine in the blood, the concentration swings associated with smoking are very large. There is even a bolus of very high and rapid increases in the arterial circulation (Henningfield, Stapleton, Benowitz, Grayson, & London 1993) coinciding with at least the first puffs from a cigarette and particularly with the first cigarette of the day. These significant peaks and valleys in the nicotine concentration of smokers produce clear psychosubjective effects that, at least for smokers, appear positive in nature. These arterial boli, or speed of delivery in general, may significantly contribute to a product's dependence potential (LeHouezec, 2003; West et al., 2000). The pharmacokinetics from a patch on the other hand can hardly under chronic use produce any psychosubjective effects. This is most likely the reason why it is very unusual to see long-term use of patch. However, cases exist (Shiffman et al., 2003) in which nicotine patch use persists. If that can be taken as an indicator of dependence, one can speculate that the type of dependence might be of a different sort than the one to cigarettes. The dependence to patch's pharmacokinetic pattern is likely to be governed by negative reinforcement, while in the dependence to cigarette smoking, there can also be considerable positive reinforcement (Fagerström, Jimenez-Ruiz, Mochales, & Gilljam, 2007).

Should Dependence Reflect Only the Contribution of the Substance or the Total Dependence?

The DSM criteria may have been intended to capture the contribution of the psychoactive substance hence the diagnostic term "nicotine dependence." The ICD term is broader: "tobacco dependence." What difference does it make? In terms of diagnosing

dependence, the systems are nearly identical. The only difference being that DSM includes "A great deal of time is spent in activities necessary to obtain nicotine." As we understand the ICD preferred term, tobacco dependence would include other substances in the tobacco with dependence potential (e.g., acetaldehyde and monoamine oxidase inhibitors; Talhout et al., 2007), but neither DSM nor ICD include or intend to measure non-pharmacological influences on dependence.

For both clinical and research purposes, capturing all factors that contribute to tobacco/nicotine dependence will likely require assessment instruments that are product specific. For cigarette smoking, these product-specific instruments exist already (e.g., the FTCD, Hooked on Nicotine Checklist [Wellman et al., 2006] and Cigarette Dependence Scale [Etter, 2008]). For other methods of tobacco/nicotine self-administration, including waterpipe, dissolvable ST, ECIGs, and NR, we suggest that product-specific scales are needed. Developing these scales will almost certainly require initial qualitative investigations in which experienced users detail use patterns, behavior, stimuli, and other features unique to the product. This initial work can then help inform item development and testing, so that the resulting instrument combines user experience with state-of-the-art understanding of dependence and sound psychometrics. For most purposes, for example, clinical, research, and legal, the total dependence (pharmacological and behavioral) is what matter most.

Conclusion

This paper has highlighted the complexities of the dependence concept as it relates to tobacco and nicotine. With cigarette smoking, the integrated complexity between the dependence-producing drug (nicotine) and nonnicotine components have been discussed. These two different components are almost impossible to disentangle, and therefore, it is suggested that diagnosing and assessing degree of dependence is best accomplished with product-specific instruments. We acknowledge that arguing for product-specific assessment instruments also has downsides. Besides the need to keep track of different scales, the comparability would be lost if instruments were created separately for each product. If a continuum of dependence is a reality, it would be of great interest to have instruments, where the score independent of product would reflect degree of dependence, that is, comparability. We acknowledge that with product-specific instruments, comparability across products may be difficult.

The other suggestion made is that when the totality of the dependence is measured, different forms of tobacco/nicotine products probably have different potential for dependence development. There might be a continuum of dependence where in one end, we find the cigarette and in the other end, NR products and particularly the patch formulation. If a particular product is far from cigarettes and close to NR on the continuum of harm and at the same time closer to cigarettes than NR on the continuum of dependence, this product may have considerable success in reducing the public health costs associated with cigarette use.

Funding

This manuscript was funded by US Public Health Service grants CA120142 and DA025659.

Declaration of Interests

None.

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