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Commentary

Determinants of Tobacco Use and Renaming the FTND to the Fagerström Test for Cigarette Dependence

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When the first version (the Tolerance Questionnaire, Fagerström, 1978) of the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991) was developed, tobacco smoking was not regarded as an addiction. Nevertheless, evidence that this might be the case was beginning to appear, and some researchers became increasingly interested in investigating the importance of nicotine in the smoking habit and educating the public about it. The research led to a profound change in the understanding of cigarette smoking, and in 1988, the U.S. Surgeon General, in the remarkable book *Nicotine Addiction*, established once and "forever" the importance of nicotine in tobacco smoking (U.S. Department of Health and Human Services [U.S. DHHS], 1988). However, as the role of nicotine was established, researchers lost sight of the possibility that other determinants might also be important. More recently, it has been found that, although nicotine is the most important addictive component of tobacco smoke, it is probably not the only substance involved in the development of tobacco dependence. In light of what is now known about what determines cigarette smoking, it seems timely to propose a renaming of the FTND to the Fagerström Test for Cigarette Dependence (FTCD). The background for this is discussed in this commentary.

Nicotine as a Determinant for Smoking

Nicotine plays a central role in tobacco use. It is a necessary condition for regular tobacco use but is it sufficient? Cigarette smoking seems to create a dependence in users as fast if not faster than other drugs (DiFranza & Ursprung, 2010) and develops to a level or degree of dependence equal to the so-called hard drugs (U.S. DHHS, 1988). Most of the effects from nicotine come from it being absorbed in the lungs and then rapidly transferred by the blood to the brain and other potential targets. The effects on the brain of nicotine delivered in this way are the primary focus of most contemporary research. However, nicotine may also have important direct effects on the peripheral nervous system. Nicotine has been found to stimulate sensory nerve endings (Ginzel, 1973), and the act of inhalation gives a strong sensorimotor stimulation in the airways. Nicotine from cigarette smoke first acts on receptors in the upper and lower respiratory airways where it causes reflex actions followed by stimulation of sensory nerves in the heart, aorta, and carotid sinus region as the drug proceeds through the circulation (Ginzel, 1975). Studies with the respiratory system have shown that the "scratch" in the throat evoked by tobacco smoke seems to be part of the rewarding pleasure derived from smoking (Levin, Rose, & Behm, 1990; Rose, Zinser, Tashkin, Newcomb, & Ertle, 1984). The results of experiments with rats suggest that this activating effect is mediated by direct rapid nervous stimulation through peripheral afferents to, for example, locus coeruleus (Comroe 1960; Tung, Ugedo, Grenhoff, Engberg, & Svensson, 1989).

The high level of dependence that develops to cigarettes and tobacco is hard to reconcile with the notion that it is solely an addiction to nicotine. Some of the evidence for this is summarized below:

a) Animals do not self-administer nicotine as readily as they do "hard drugs" like amphetamine, cocaine, and heroin (Villegier, Blanc, Glowinski, & Tassin, 2003).
b) Nicotine is also a relatively weak reinforcer in human laboratory studies (Hughes, Rose, & Callas, 2000; Perkins, Gerlach, Broge, Fonte, & Wilson, 2001)
c) 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, Acosta, Evans, Breland, & Eissenberg, 2005; Donny, Houtsmuller, & Stitzer, 2007) and alters brain nicotinic acetylcholine receptor occupancy (Brody et al., 2009). The so-called "scratch" in the throat may be of importance for these effects.
d) Although nicotine replacement treatment is an effective aid for quitting smoking, its efficacy is moderate (Fiore et al., 2008) even if doses that replace most or all nicotine from the cigarettes are used (Dale et al., 1995).
e) There is no evidence for the abuse of pure nicotine.

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Pharmacological Determinants for Smoking Other Than Nicotine

Tobacco seems to have additional effects beyond nicotine. In the trivial sense, tobacco smoke is made up of thousands of chemicals. The more interesting question is whether any of these also contributes to reinforcing properties of tobacco smoke. It has been known for some time that cigarette smoke inhibits monoamine oxidase (MAO), the enzyme that catalyses the metabolism of monoamine neurotransmitters, such as dopamine, thus potentiating their effects in the brain of smokers and thereby contributing significantly to reward and dependence (Fowler et al., 1999, 2003). Nicotine is not directly responsible for this effect (Fowler et al., 1999). Acetaldehyde, an established constituent of tobacco smoke, is a potent inhibitor of MAO (both the A and the B subtypes), and it has been suggested that this compound causes the MAO inhibition. In experimental rats, nicotine self-administration is enhanced when the animals are also treated with acetaldehyde. Other studies suggest that the condensation products of acetaldehyde, salsolinol, and the harmans are more likely candidates as the inhibitors MAO. Salsolinol (Rodd et al., 2003) and harmans (Baum, Hill, & Rommelspacher, 1996) are also themselves directly rewarding in rats. Other tobacco-containing alkaloids, like myosmine, anatabine, anabasine and nornicotine, also seem to have rewarding effects in the sense that they substitute for nicotine in drug discrimination tests, increase nicotine self-administration (Clemens, Cailille, Stinus, & Cador, 2009), and reduce avoidance to noxious stimuli (Holtman, Crooks, Johnson-Hardy, & Wala, 2010).

Nonpharmacological Determinants

Until relatively recently, cigarette smoking was regarded as simply a strong habit, and many smokers still hold that view. Is it possible that in pursuing the search for the mechanisms underpinning the dependence upon nicotine and tobacco, researchers may have overlooked the other aspects of the smoking habit that may also be important. These could include:

a) The habit and conditioning associated with smoking
b) The role of the object—that is, the cigarette itself
c) The psychosocial aspects of smoking.

Habit and Conditioning

The half-life of nicotine is short, about 2 hr, and it is even shorter for many of the other pharmacologically active substances found in tobacco smoke. That necessitates frequent administration in order to obtain both its negative or positive reinforcing effects. Thus, in order to maintain the desired levels of nicotine and the other components of tobacco smoke, the smoker repeats smoking-associated behavior (e.g., taking the cigarette out of the pack, maybe 15 times/day, lighting it, holding it for 5–10 min, and inhaling the smoke 10 times/cigarette) many times each day. Each inhalation gives a sensory impact, first in the mouth followed by the throat and the lungs and finally the exhalation through mouth and or nose. This entire procedure can be relaxing by itself although the inhalation and exhalation of tobacco smoke seems to be especially important (McClernon, Westman, & Rose, 2004). It is not inconceivable that all these behaviors are difficult to break in themselves. Behaviors without chemical reinforcers such as nail biting, betting, and computer gaming can be hard to break and can be associated with withdrawal symptoms when trying to stop (Gilbert, Gilbert, & Schultz, 1998). Also nonsubstance addictions like pathological gambling seem to share the same brain functioning mechanisms as drug addictions (van Holst, van den Brink, Veltman, & Goudriaan, 2010). Maybe these activities share some commonalities with obsessive compulsive behaviors that are anxiety reducing and anxiety provoking when inhibited. Since smoking is relatively ritualized, that is, takes place in mostly the same situations, conditioning occurs such that stimuli by themselves can elicit craving responses. This is supported by the evidence that nicotine self-administration in rats is greatly enhanced when paired with nicotine-associated stimuli such as light (Caggiula et al., 2009). Although nicotine may be necessary in or at least facilitating the early conditioning of pleasure and craving for certain stimuli, it is possible that, with frequent repetition, these stimuli become very resistant to extinction. It is noteworthy that nonnicotine cigarettes are preferred to nicotine-containing gum and relieves withdrawal symptoms better for the periods (weeks) that it has been studied (Barrett, 2010; Buchhalter et al., 2005; Donny et al., 2007).

The Cigarette as an Object

The cigarette looks very much the same today as hundred years ago from brand to brand and country to country. This suggests that its shape, from color and size, has some appeal. It is soft, warm, and comfortable to hold and put to the lips. Although very little research has explored the rewarding effects of just handling and manipulating a cigarette, it may not be unreasonable to believe that it can contribute somewhat to the pleasant smoking experience. If the cigarette has any similarities to the function of a pacifier is not known but not completely implausible. Whether the cigarette box, lighter, or matches too have any rewarding function is even less clear. Anecdotally, patients report that holding and caressing their cigarette pack can give some relief of stress.

Cigarette Smoking and Psychosocial Functions

Cultural drugs in general have psychosocial functions. We often drink coffee and alcohol together, and it can function as a lubricant for social behavior. That is true also for smoking. Offering a cigarette can be a means by which one contacts an unknown person. It can be a reason to take a break or pause from a boring task sometimes together with other smokers. This has the potential to increase bonding and togetherness. When caught on the spot, lighting a cigarette gives a smoker some time to formulate thoughts. Although smoking today in many cultures is disproved of, there are still cultures or subcultures where smoking makes the smoker identify and conform with others. It can stimulate activities with its rewarding properties (have to finish this before I can have a cigarette), be a "friend" when an individual is lonely, and in certain circumstances, smoking gives the hands something to do and, in doing so, diminish anxiety.

Smoking as a Broad Complex Dependence

It should come as no surprise that stopping use of nicotine replacement, with its much less behavioral involvement, is easier to do than stopping cigarettes. Also there are differences in the ways in which different nicotine replacement products are used. While there is almost no long-term use of patches, it is not so uncommon with nicotine gum. Also, it seems that quitting smokeless tobacco, which has fewer behavioural components and is a more solitary thing than smoking, is easier than stopping smoking (Fagerström, Gilljam, Metcalfe, Tonstad, & Messig, 2010). One of the reasons that it is as difficult to stop smoking as it is to stop use of hard drugs that usually are stronger reinforcers may be because of the contribution of the nonnicotine factors discussed above. An analogy with caffeine may be useful to explain why smokers prefer a reduced nicotine cigarette over one with normal nicotine concentration. Consider the case of a regular and frequent coca cola user who becomes tired and thirsty and longs for a cold coke but is offered a hot cup of coffee. If the primary motivation to drink coca cola is to get caffeine, the hot cup of coffee should do as well. Most likely, the coke drinker will entirely refuse the hot coffee as much as most smokers wanting a cigarette reject a nicotine gum. This occurs partly because the craving for the coke and cigarette is not just about the drug but also includes all the other features that go with the respective objects. The much more rapid nicotine delivery from cigarettes may also contribute to the higher dependence potential with cigarettes. The pH of modern cigarettes is so low that it almost requires inhalation into the lungs for effective nicotine absorption. The design of the filter also enables very close titration of nicotine.

Shifting Orientation From Nicotine to Tobacco

Many clinical researchers, epidemiologists, and clinicians when working with cigarette smoking and smokers often use the term "nicotine dependence" to describe their work, although what they are studying is tobacco smoking. Apart from using a too narrow term, it also may send signals like it is nicotine that is the problem. Nicotine is not the major problem from a health point of view. Pure or medicinal nicotine is probably not that much different from caffeine and certainly less dangerous than alcohol. Nicotine is a strong determinant for dependence, but dependence to cigarette smoking is a multifaceted and broad dependence. Nicotine can also to some degree be part of the solution to the smoking problem if the need for tobacco smoking could be substituted by pure nicotine. What should be highlighted as the problem is tobacco and particularly smoked tobacco. Cigarettes smoke causes both the physical diseases and the strong dependence. It is also worth noting that in the International Classification of Diseases and Injuries by World Health Organization (World Health Organization, 1993) contrary to the American Psychiatric Association's (1994) *DSM* system , the term "tobacco dependence" is used rather than nicotine dependence. Emphasizing tobacco does not mean that nicotine should be ignored. It remains an integral component of tobacco.

When renaming the FTND, should it be Fagerström Test for Tobacco Dependence or FTCD? Tobacco comes in many forms like cigarettes, water pipe, cigars, smokeless tobacco, and pipe smoking among many others. These products are obviously very different not only in their physical characteristics but also in the cultural norms and prescriptions that are surrounding them. The total dependence panorama will most likely vary from a cigarette smoker to someone who uses tobacco in a different form, for example, a smokeless tobacco (Fagerström et al., 2010). A general questionnaire for tobacco dependence would need to be validated against all forms of tobacco use from cigarettes to smokeless tobacco. That has not been done with the FTND, and moreover, most of the questions in the questionnaire relate specifically to smoking behavior. Therefore, it seems appropriate to rename the FTND the Fagerström Test for Cigarette Dependence.

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