

Nicotine Salts and Synthetic Nicotine: New Challenges for an Old Problem

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Sais de Nicotina e Nicotina Sintética: Novos Desafios para um Velho Problema

Sales de Nicotina y Nicotina Sintética: Nuevos Desafíos para un Viejo Problema

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INTRODUCTION

Tobacco use is a chronic disease caused by nicotine dependence found in tobacco products associated with innumerable diseases¹. It is also a pediatric disease because the majority of smokers began smoking in childhood and adolescence^{2,3}.

Since 2004, the treatment for tobacco cessation is offered by the National Health System (SUS) in all its complexity levels⁴. However, studies of pharmacologic approach for adolescents are scarce and inaccurate⁴. This population is the most influenceable to becoming a smoker and suffer the consequences of exposure to nicotine, further to be the target of strategies to lure them, as ads, new attractive products⁶ and additives that grant tobacco products a combination of flavors of candies and sweets⁷.

In this context, further to the already known challenges of tobacco use treatment, the utilization of other forms of nicotine and the development of commercially viable forms of synthetic nicotine can impact the treatment for smoking cessation and tobacco control policies.

The objective of this article is to discuss new forms of nicotine and their impact.

DEVELOPMENT

NICOTINE SALTS

Nicotine can be found in three forms: free-base (FbNic), monoprotonated and diprotonated. FbNic is volatile and gaseous while protonated nicotine is non-volatile. The liquids utilized in first generation Electronic Smoking Devices, the e-cigarettes, were basically formed by pure FbNic dissolved in a mixture of propylene glycol and/or glycerol. Aerosols formed by liquids of FbNic provoke harshness which reduces the concentrations of nicotine that can be utilized⁸.

The harshness can be reduced by adding an acid in the mixture of propylene glycol and/or glycerol, the benzoic acid used in 4th generation e-cigarettes with PODs (a cartridge containing nicotine) is an example⁸. This nicotine is known as nicotine salt (NicSalt).

This strategy allows products like JUUL to deliver nicotine concentrations 20 times larger than other free-base e-cigarettes formulations¹⁰, without, however, causing the same impact of harshness in the mouth and throat expected for this level of nicotine concentration. In addition to the higher potential addictiveness compared to other e-cigarettes, NicSalt provokes a physiologic reaction to the user similar to conventional cigarettes^{10,11}.

FbNic is more volatile and possibly oral mucosa tends to absorb it at higher levels, but on the other hand, buccal and throat harshness is larger and absorption by the lungs is slower. After adding benzoic acid (or other similar acids) to FbNic, NicSalt are formed which favors the consumption of higher doses of nicotine but less harsh to the throat^{10,11} and despite slower oral absorption, lung absorption is faster¹². Later, other manufacturers started to utilize NicSalt in their products^{10,11}.

The entry of the products containing NicSalt into the market had so huge impact that in 2018, the USA Surgeon General stated that the use of E-cigarettes is an epidemic among young adults¹³.

The phenomenon can be, in part, explained by the possibility of using nicotine concentrations previously impossible to use, due to the impact caused in the throat and mouth and by the optimization of delivery, bioavailability, attractiveness, and reduction of harshness caused by nicotine, which is modulated by the ratio of nicotine forms. In this context, the higher proportion of NicSalt in relation to NicBL is less harsh than the reverse proportion¹⁴.

A POD (cartridge containing nicotine extract utilized in some e-cigarettes) contains an amount of nicotine

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equivalent to a pack of regular cigarettes⁹. Studies suggest that this type of nicotine can be more addictive than nicotine found in regular cigarettes, additionally, other investigations indicated a possible risk increase of future use of traditional cigarettes and marijuana¹⁵⁻¹⁸.

To the best of the existing knowledge, no guidelines to treat e-cigarettes-dependent young adults exist. Well-succeeded pharmacological methods to help adults to quit smoking were not tested yet for the young population¹⁹.

There is some discussion about the possibility of these devices being used as tools for smoking cessation, some studies suggest a possible increase in cessation rates²⁰ and manufacturers²¹ claim e-cigarettes are less toxic when compared to conventional cigarettes. However, studies indicate that these devices, in addition to the possible health harms, can lead to sustained nicotine dependence^{22,23}. The fact that new electronic cigarette versions have optimized forms of nicotine delivery and attractive design, with more than 8,000 flavors and 250 brands in the United States alone²⁴, among other factors, enhance their ability to attract the public, especially younger people and non-smokers^{6,10,19}.

SYNTHETIC NICOTINE

More recently, chemically processed synthetic nicotine, and the offer of related products has drawn increased attention as they are meant to cause similar effects of tobacco-derived nicotine. Usually, synthetic nicotine is only available as a racemic mixture, containing both *S*-nicotine and *R*-nicotine, different from the natural *S*-nicotine²⁵.

R and *S* nicotine are distinct chemical substances but with identical physic-chemical properties^{25,26}. However, its pharmacological effects are different in human beings. The form *S* is responsible for dependence and its epidemiologic, pharmacologic and biologic effects are well studied^{27,28}. On the other hand, the effects of the form *R* are scarce. Studies with animals suggest greater effect of the natural form *S* on brain tissue^{29,30}.

Tobacco industry (TI) documents revealed that the industry considered the use of synthetic nicotine in 1960-1970, but at that time, TI believed *S*-nicotine extracted from the plants more economical, and probably more efficient³¹⁻³³.

In the past, synthetic nicotine was 50-fold more expensive than natural nicotine, but today, it is 4-fold only. One liter of tobacco-extracted nicotine is valued approximately at US\$ 400, and synthetic, US\$ 1,800^{34,35}.

One of the possible objectives to utilize synthetic nicotine is the reduction of the agricultural burden to produce natural tobacco as quoted by Rossel²⁶ and suggested by tobacco industry documents mentioned earlier.

Another issue deserving additional studies is the interference or optimization of nicotine-dependence caused by other alkaloids found in tobacco leaves. Notwithstanding studies with mice suggesting a potential optimization of alkaloids as anatabine, cotinine and myosmine³⁶, the effects of these alkaloids on nicotine-dependence and the consequences of synthetic nicotine in humans with or without these components is unknown.

The manufacturers of these products can explore gaps in certain legal frameworks because historically, many countries created their regulations based on tobacco products. As an example, the United States Congress, in March 2022, had to approve legislation that determined that the USA Food and Drug Administration (FDA)³⁷ has the mandate to regulate these products, until then, not been part of the FDA scope. In the case of Brazil, the Brazilian laws 9,294/1996³⁸ and 9,782/1999³⁹ addressed those products due to the language used that includes tobacco and non-tobacco products.

CONCLUSION

The new forms of nicotine associated with attractive designed products, particularly for young individuals bring considerable technical challenges for health professionals because, so far, there are no effective protocols for these populations to treat nicotine-dependence resulting from this new forms of consumption.

Likewise, specific protocols even for traditional nicotine-dependence for this age-range, the predominant user of these products, are scarce.

Thus, any regulation concerning these products must be analyzed cautiously because, to date, nicotine addiction caused by these forms needs more treatment protocols, especially for younger people, making it difficult to face. Contrary to what is advertised, the scientific literature shows that this product, initially intended for adult smokers, is especially attractive to young people who have never used tobacco before.

Still, even if, arguably, these products may be less toxic when compared to traditional ones, the possibility that their impacts are even more damaging, should not be neglected because, in addition to the hypothesis of an until unknown intensity dependence, there is the potential to lure persons who had never smoked in their lifetime and eventually provoking nicotine-dependence.

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André Luiz Oliveira da Silva contributed substantially to the study design, acquisition, analysis and interpretation of the data and critical review. Josino Costa Moreira contributed substantially to the acquisition, analysis and interpretation of the data, wording and critical review. Both authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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