



E-cigarettes and tobacco heaters – a healthier alternative or another threat. Literature review

E-papierosy i podgrzewacze tytoniu – zdrowsza alternatywa czy kolejne zagrożenie? – przegląd literatury

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■ Abstract

Introduction and Objective. Nicotinism has been one of the most common addictions for many years. Tobacco smoking, both active and passive, is a serious social problem. In recent years, alternatives to conventional cigarettes have appeared on the market. The aim of the review is to analyze the latest publications available in PubMed and Google Scholar on the impact of e-cigarettes and tobacco heaters on health, in comparison with conventional tobacco products.

Brief description of the state of knowledge. The commonly prevailing myth about the lower harmfulness of these products is being refuted more and more often. In many cases, they have a similar effect to traditional cigarettes on the organs, *inter alia* interfering with the functioning of the circulatory and respiratory systems. Due to the high concentration of nicotine, they can interfere with the development of the central nervous system, and their impact on fertility has also become the subject of research. It is extremely important for the health of the young generation due to the increasingly frequent use of these products by adolescents and young adults. E-cigarettes are not without impact on health and although in some aspects they may cause less organ toxicity than traditional cigarettes, it is extremely disturbing that they can lead to diseases that were not previously associated with nicotinism, e.g. by disturbing the proper functioning of the liver.

Summary. When reviewing scientific papers, many ambiguities and even contradictions in the assessment of the risk of using these products are still found. Although the overall assessment of health effects indicates their possible harmfulness, their potential use in the treatment of nicotinism cannot be overlooked.

■ Key words

smoking cessation, nicotine, electronic cigarettes, nicotinism, tobacco heaters

■ Streszczenie

Wprowadzenie i cel pracy. Nikotynizm od lat jest jednym z najczęściej występujących uzależnień, a palenie tytoniu – zarówno bierne, jak i czynne – stanowi poważny problem społeczny. W ciągu ostatnich lat pojawiły się na rynku produkty alternatywne dla konwencjonalnych papierosów. Celem pracy jest przegląd i analiza najnowszych, dostępnych w PubMed oraz Google Scholar, publikacji na temat wpływu e-papierosów oraz podgrzewaczy tytoniu na zdrowie w porównaniu z konwencjonalnymi wyrobami tytoniowymi.

Opis stanu wiedzy. Coraz częściej obala się powszechnie panujący mit o mniejszej szkodliwości tych wyrobów w porównaniu z tradycyjnymi papierosami. Okazuje się, że mają one podobny jak one wpływ na narządy, zaburzając m.in. funkcjonowanie układu krążenia czy układu oddechowego. Ze względu na wysokie stężenie nikotyny mogą zaburzać rozwój ośrodkowego układu nerwowego. Przedmiotem badań stał się też ich wpływ na płodność, co jest niezwykle istotne dla zdrowia młodego pokolenia z powodu coraz częstszego sięgania po te produkty przed młodzią i młodych dorosłych. Nie pozostają one bez wpływu na zdrowie i choć w pewnych aspektach mogą powodować mniejszą toksyczność narządową niż tradycyjne papierosy, to niezwykle niepokojący jest fakt, że mogą prowadzić do chorób, które wcześniej nie były kojarzone z nikotynizmem, np. poprzez zaburzenie prawidłowej pracy wątroby.

Podsumowanie. Dokonując przeglądu prac naukowych, ciągle stwierdza się wiele niejasności, a nawet sprzeczności w ocenie ryzyka korzystania z tych wyrobów. I choć całościowa ocena skutków zdrowotnych korzystania z e-papierosów

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i podgrzewaczy tytoniu wskazuje na ich możliwą szkodliwość, to nie można pominąć ich potencjalnego zastosowania w leczeniu nikotynizmu.

Słowa kluczowe

zaprzymanie palenia, nikotyna, papierosy elektroniczne, nikotynizm, podgrzewacze tytoniu

INTRODUCTION AND OBJECTIVE

Nicotine addiction impacts many individuals. Cigarettes are smoked by both adolescents and adults across all age groups. Despite numerous large-scale anti-smoking campaigns aimed at raising awareness about the health risks that may have both individual and social consequences, smokers remain addicted for many years. A significant number express the desire to quit smoking, yet these attempts often prove ineffective.

In recent years, alternatives to traditional cigarettes have entered the market: e-cigarettes and tobacco heaters. The assumption was that these products are less harmful. Their attractiveness – if only because of the lack of the unpleasant smell typical of conventional tobacco products, as well as easy availability – contributed to their growing popularity.

The aim of the review is to assess the latest information available in scientific articles on the health impact of e-cigarettes and tobacco heaters.

MATERIALS AND METHOD

A review was conducted of the available literature on the impact of e-cigarettes and tobacco heaters on health. Selected key words were used for this purpose. Focus was on the latest publications in order to select the most up-to-date information.

DISCUSSION

The first e-cigarette (EC) was created in 2003 by Hon Lik, a Chinese pharmacist [1]. Since then, this alternative source of nicotine has grown significantly in popularity, entering both the American and European markets. Initially, this new product was believed to be less harmful than conventional cigarettes, however; due to the lack of knowledge about the long-term health impact, in 2008 the WHO banned the promotion of e-cigarettes as a healthier alternative, underscoring the need for further research [2].

The main difference between e-cigarettes and conventional tobacco products is the fact that the former do not burn tobacco [3], due to the different construction of the e-cigarette which consists of a supply system and a vaporizing system. By heating the liquid to a temperature enabling the transition from the liquid phase to the gas phase, an aerosol is created. According to most authors, it is devoid of tar substances produced during smoking traditional cigarettes. However, the aerosol inhaled while using e-cigarettes may contain toxic substances, such as acetaldehyde, acetone, acrolein, formaldehyde and nicotine – the latter is also highly addictive [2]. Additional substances to which e-cigarette users are also exposed are glycerol or propylene glycol, which are solvents for other substances and may cause irritation (including respiratory tract) and contact allergies [4]. It is worth noting, however, that the content of e-cigarettes is devoid of heavy

metals. There are studies showing deviations between the declared and actual composition of e-cigarette liquid [4].

According to the Polish Journal Laws, article 276 (DZ.U.2021.276), it is illegal to provide electronic cigarettes to individuals under the age of 18; however, in practice the sale is still unsupervised and accessible to minors. There are also documented cases of inadvertent poisoning caused by the consumption of e-liquid because of the high dose of nicotine. The belief in the harmlessness of these products only amplifies the risk [5].

Currently, more and more attention is being paid to the adverse health effects of e-cigarettes; the symptoms which the addicted person might initially fail to associate with their use, include headache, dizziness, nausea, vomiting or insomnia. Particularly noteworthy is the harmful effect of nicotine on the circulatory system – it causes vasoconstriction and, consequently, an increase in blood pressure, accelerated and irregular heart rhythm, and an increase in the risk of thrombosis. It is also a carcinogenic substance [3].

In recent years, numerous studies have been conducted to determine the impact of e-cigarettes on oral health. The results of epidemiological studies highlight the increased risk of dry mouth, mucosal irritation, tooth decay and gum disease in e-cigarette smokers [6, 7]. In addition, studies have shown reduced expression of suppressor genes, genes related to immunity and genes responsible for DNA repair in the epithelium of both the oral and nasal cavities in e-cigarette users [7].

E-cigarettes affect the respiratory system and can cause irritation of the upper respiratory tract, dry cough and allergic inflammation [1]. There is also growing experimental evidence showing a link between e-cigarette use and the incidence of chronic obstructive pulmonary disease (COPD) and asthma. Furthermore, vaporization weakens the immune responses in the lungs, increasing the risk of infection. Importantly, the risk of contracting COVID-19 by e-cigarette users was five times higher [7].

Currently, there is a visible tendency among adolescents and young adults to replace conventional tobacco products with e-cigarettes. The rising popularity is significantly influenced by a wide selection of different flavours and fragrances, in particular sweet flavours such as fruit or chocolate. Analysis of this problem leads to the conclusion that the elimination of flavoured e-cigarettes could reduce their use among adolescents [8]. Companies that produce and sell e-cigarettes target young people in their marketing, with advertisements widely available on social media. Studies (admittedly based on conventional cigarettes, but the e-cigarettes discussed in this review also contain high concentrations of nicotine) reveal the dangerous effect of nicotine on the central nervous system of teenagers, which may result in memory impairment, cognitive deficits or hyperactivity [9].

There are also studies that prove the increased risk of using conventional cigarettes in the future by people previously addicted to e-cigarettes [9].

The problem of second hand smoking is also worth analyzing – its harmfulness has been known for years, which

is confirmed by studies showing an increased risk of stroke, hypertension and cancer in passive smokers of conventional cigarettes [10]. Therefore, it is necessary to consider what impact the use of e-cigarettes has on people in the environment, taking into account the change in stereotypical behaviour of e-cigarette smokers, who very often smoke in closed rooms, such as at homes, cars, or workplaces. This fact is still the subject of research and analysis. When reviewing the literature, one can find works indicating that people passively exposed to e-cigarette vapors are exposed to pollutants at levels above the background, and in concentrations that may have potentially harmful effects on health [11]. However, there are also studies showing that the level of harmful substances in the aerosol exhaled while using an e-cigarette is below regulatory standards, and does not indicate a risk to bystanders [12].

Recently, reports have surfaced about the harmful effects of e-cigarettes on reproductive health; however, these studies have been conducted primarily in animal models. In order to be able to unequivocally comment on this subject, it would be necessary to conduct clinical trials, but nonetheless, couples trying to conceive should be aware of the potential threat. A preliminary study, the results of which were presented at the British Fertility Society conference in 2017, showed a significant decrease in the motility of sperm cultured with the addition of aroma to liquids. Animal studies have shown a reduced percentage of normal follicles in the ovaries of female rats exposed to e-liquid. It is also suggested that a toxic effect on the male foetus developing in the uterus may be possible, reducing its fertility in the future. Low body weight has also been reported in fetuses of both genders, and impaired lung development, increased body weight or behavioral disorders in passively exposed newborns [13].

The second, newer, and recently extremely fashionable and overused alternative to conventional cigarettes are heat-not-burn (HNB) tobacco heating systems (THS) of heated tobacco products (HTP). The first IQOS devices by Philip Morris appeared on the US market in 2019. The operation of HNB electric devices consists in heating tobacco to a temperature of 350°C. A tobacco unit is made from ground tobacco leaves and visually resembles a short cigarette [14].

According to the US Food and Drug Administration (FDA), there are four substances potentially carcinogenic to humans in the IQOS aerosol, and nine other substances raise toxicological concerns, mainly acids, aldehydes, ketones, furans, pyrrole, pyridine and quinoline. Furthermore, as in the case of e-cigarettes, tobacco heaters are often used in small rooms with limited ventilation, which can potentially cause the accumulation of harmful compounds such as acetaldehyde or nicotine [15]. Studies conducted on current HNB smokers have shown a similar effect of these tobacco products on the cardiovascular system as in the case of conventional cigarettes: they contribute to an increase in blood pressure, heart rate, and finally an increase in arterial stiffness [16]. In randomized studies, HNB products, like traditional cigarettes or e-cigarettes, increase oxidative stress; however, the dysfunction of the vascular endothelium they cause is significantly lower than in the case of the former [16]. Heated tobacco products users have a lower HDL-C cholesterol concentration, which is lower than in people who have never smoked, but higher than in smokers of traditional cigarettes [17].

Research is also underway on the effects of tobacco heaters on the respiratory system. It has been shown that inhalation

of the IQOS aerosol leads to an increase in the number of pro-inflammatory cells in the lungs and to damage to the lung epithelial cells [18]. Acute lung dysfunction has also been documented immediately after using HNB products. It may result from bronchospasm, swelling of the mucous membrane or excessive secretion in the respiratory tract [19]. An *in vitro* study conducted on human bronchial epithelial cells showed a higher cytotoxicity of HNB aerosol compared to e-cigarette aerosol, but less than smoke from conventional cigarettes [20].

The impact of these products on other organs is also under investigation. Both humans and animals studies have shown possible hepatotoxic effects that have not been seen after exposure to cigarette smoke. After a 5-day exposure to the IQOS aerosol, the level of bilirubin was three times higher than in abstainers [21]. In combination with alcohol, which is often abused by smokers, and hepatotoxic drugs, such as paracetamol, it can have a dangerous effect on the functioning of the liver.

The scientific community is also examining the impact of tobacco heaters on oral health. Previous studies have not shown toxicity to oral fibroblasts and keratinocytes [22], however, long-term effects need to be monitored. Beneficial changes in the course of chronic generalized inflammatory periodontitis have been observed and described in people who stopped smoking cigarettes and switched to HNB products [23].

As in the case of e-cigarettes, adolescents and young adults are most susceptible to addiction to tobacco heaters [24]. In July 2020, the FDA extended the authorization to trade in the IQOS product as a product causing reduced exposure to harmful and potentially harmful toxic substances compared to traditional cigarettes [25]. According to the manufacturer of IQOS, their target market is current cigarette smokers [26], but it is extremely concerning that tobacco heaters are often used (sometimes even more willingly) by people who have not used tobacco products before [27]. These products are more often purchased by men than women [28]. Unfortunately the use of HTP often becomes an addition and not a replacement for traditional cigarettes, another way of delivering nicotine, which consequently reduces the likelihood of quitting the addiction [29].

There are increasing calls for the ban on smoking in public places to apply equally to e-cigarettes and traditional cigarettes [30].

Finally, it is worth discussing the role of e-cigarettes in stopping smoking. Quitting this addiction is beneficial for health at any age, and making this decision before the age of 40 reduces the risk of death related to continued smoking by about 90% [31]. Analyzing scientific publications, information is found on greater satisfaction from quitting smoking using e-cigarettes than nicotine replacement therapy (NRT), which results from the pleasant taste of these products as well as their shape, which allows maintaining the sensations and reflexes similar to conventional smoking [32].

Addicts who decided to stop smoking with the use of e-cigarettes managed to maintain abstinence longer than in the case of a group of people using only NRT products available without a prescription [33]. Despite the potential use of using e-cigarettes to quit smoking, this topic requires further research due to the previously presented, possible negative effects associated with their use. Moreover, the risk of simultaneous use of e-cigarettes and conventional

cigarettes as a result of a failed attempt to quit smoking cannot be ignored, which in turn may lead to even more adverse effects [32].

CONCLUSIONS

Regrettably, both types of presented products – undoubtedly attractive, especially for young people and widely available and becoming more and more popular – provide the body with highly addictive nicotine, leading to the need for regular smoking, which in turn may end in nicotine addiction and reaching for conventional cigarettes.

Currently, there is still a lack of studies assessing the long-term health effects of using e-cigarettes and tobacco heaters, and a more accurate comparison of the harmfulness of these products. There is also no evidence that replacing conventional cigarettes with their more modern counterparts will significantly reduce the number of tobacco-related diseases. The possibility of causing other, hitherto unknown organ damage also requires further analysis.

While the new products can satisfactorily replace the smoking experience and reduce exposure to toxic substances, they are not completely safe for health and are not an ideal alternative to cigarettes or as a quitting aid – possibly leading to concomitant use of conventional tobacco products and their newer alternatives.

The risk of using e-cigarettes or tobacco heaters by people who have not previously smoked should be emphasized, taking into account the fact that this decision may be conditioned by fashion or the belief that these products are harmless.

REFERENCES

- Zdrojewicz Z, Pypno D, Bugaj B, et al. Elektroniczne papierosy: wpływ na zdrowie, nikotynowa terapia zastępcza, regulacje prawne. *Pediatr Med Rodz.* 2017;13(1):63–71. <https://doi.org/10.15557/PiMR.2017.0006>
- Stępniewska A, Kowalczyk M, Cholewińska E, et al. E-papierosy – pomoc w rzuceniu palenia czy zagrożenie? *HYG.* 2017;52(2):86–95.
- Zielonka T. A Debate: Can We Recommend Electronic Cigarettes to Our Patients? *Opinion 1. Adv Respir Med.* 2017;85:3539. <https://doi.org/10.5603/ARM.2017.0007>
- Kucharska M, Wesołowski W, Czerczak S, et al. Badanie składu płynów do e-papierosów – deklaracje producenta a stan rzeczywisty w wybranej serii wyrobów. *Med Pr.* 2016;67(2):239–253. <https://doi.org/10.13075/mp.5893.00365>
- Gomółka E, Radomska M, Bielska E. Ostre zatrucie płynem do e-papierosów – opis przypadku. *Prz Lek.* 2016;73(10):795–797.
- Holliday R, Chaffee BW, Jakubovics NS, et al. Electronic Cigarettes and Oral Health. *J Dent Res.* 2021;100(9):906–913. <https://doi.org/10.1177/00220345211002116>
- Gordon T, Karey E, Rebuli M, et al. E-Cigarette Toxicology. *Annu Rev Pharmacol Toxicol.* 2022;62(2):301–322. <https://doi.org/10.1146/annurev-pharmtox-042921-084202>
- Harrell MB, Weaver SR, Loukas A, et al. Flavored e-cigarette use: Characterizing youth, young adult, and adult users. *Prev Med Rep.* 2017;5:33–40. <https://doi.org/10.1016/j.pmedr.2016.11.001>
- Jones K, Salzman GA. The Vaping Epidemic in Adolescents. *Mo Med.* 2020;117(1):56–58.
- Whanhee L, Sung-Hee H, Hayoung Ch, et al. The association between smoking or passive smoking and cardiovascular diseases using a Bayesian hierarchical model: based on the 2008–2013 Korea Community Health Survey. *Epidemiol Health.* 2017;22(39). <https://doi.org/10.4178/epih.e2017026>
- Hess I, Lachireddy K, Capon A. A systematic review of the health risks from passive exposure to electronic cigarette vapour. *Public Health Res Pract.* 2016;26(2). <http://dx.doi.org/10.17061/phrp2621617>
- O'Connell G, Colard S, Cahours X, et al. An Assessment of Indoor Air Quality before, during and after Unrestricted Use of E-Cigarettes in a Small Room. *Int J Environ Res Public Health.* 2015;12(5):4889–4907. <https://doi.org/10.3390/ijerph120504889>
- Montjean D, Godin Page MH, Belanger MC, et al. An Overview of E-Cigarette Impact on Reproductive Health. *Life.* 2023;13(3). <https://doi.org/10.3390/life13030827>
- Fried N, Gardner J. Heat-not-burn tobacco products: an emerging threat to cardiovascular health. *Am J Physiol – Heart Circ.* 2020;319(6):1234–1239. <https://doi.org/10.1152/ajpheart.00708.2020>
- Uguna C, Snape C. Should IQOS Emissions Be Considered as Smoke and Harmful to Health? A Review of the Chemical Evidence. *ACS Omega.* 2022;7(26):22111–22124. <https://doi.org/10.1021/acsomega.2c01527>
- Fried N, Gardner J. Heat-not-burn tobacco products: an emerging threat to cardiovascular health. *Am J Physiol – Heart Circ.* 2020;319(6):1234–1239. <https://doi.org/10.1152/ajpheart.00708.2020>
- Hu H, Nakagawa T, Honda T, et al. Heated tobacco products and circulating high-density lipoprotein cholesterol concentrations. *Sci Rep.* 2022;12:17385. <https://doi.org/10.1038/s41598-022-22337-3>
- Bhat T, Kalathil S, Leigh N, et al. Acute Effects of Heated Tobacco Product (IQOS) Aerosol Inhalation on Lung Tissue Damage and Inflammatory Changes in the Lungs. *Nicotine Tob Res.* 2021;23(7):1160–1167. <https://doi.org/10.1093/ntr/ntaa267>
- Pataka A, Kotoulas S, Chatzopoulos E, et al. Acute Effects of a Heat-Not-Burn Tobacco Product on Pulmonary Function. *Medicina (Kaunas).* 2020;56(6):292. <https://doi.org/10.3390/medicina56060292>
- Leigh N, Tran P, O'Connor R, et al. Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells. *Tob Control.* 2018;27:26–29. <https://doi.org/10.1136/tobaccocontrol-2018-054317>
- Chun L, Moazed F, Carolyn C, et al. Possible hepatotoxicity of IQOS. *Tob Control.* 2018;27:39–40. <http://dx.doi.org/10.1136/tobaccocontrol-2018-054320>
- Pagano S, Negri P, Coniglio M, et al. Heat-not-burn tobacco (IQOS), oral fibroblasts and keratinocytes: cytotoxicity, morphological analysis, apoptosis and cellular cycle. An in vitro study. *J Periodont Res.* 2021;56(5):917–928. <https://doi.org/10.1111/jre.12888>
- Pouly S, Ng W, Benzimra M, et al. Effect of Switching to the Tobacco Heating System Versus Continued Cigarette Smoking on Chronic Generalized Periodontitis Treatment Outcome: Protocol for a Randomized Controlled Multicenter Study. *JMIR Res Protoc.* 2021;10(1):e15250. <https://doi.org/10.2196/15350>
- Czoli Ch, White Ch, Reid J, et al. Awareness and interest in IQOS heated tobacco products among youth in Canada, England & the United States. *Tob Control.* 2020;29(1):89–95. <https://doi.org/10.1136/tobaccocontrol-2018-054654>
- Barker J, Vassey J, Chen-Sankey J, et al. Categorizing IQOS-Related Twitter Discussions. *Int. J. Environ. Res. Public Health.* 2021;18(9):4836. <https://doi.org/10.3390/ijerph18094836>
- Levine H, Duan Z, Bar-Zeev Y, et al. IQOS Use and Interest by Sociodemographic and Tobacco Behavior Characteristics among Adults in the US and Israel. *Int J Environ Res Public Health.* 2023;20(4):3141. <https://doi.org/10.3390/ijerph20043141>
- McKelvey K, Popova L, Kim M, et al. Heat-not-burn tobacco products: concerns from the Italian experience. *Tob Control.* 2018;27:41–47. <http://dx.doi.org/10.1136/tobaccocontrol-2017-054054>
- Dai H. Heated Tobacco Product Use and Associated Factors Among U.S. Youth, 2019. *Drug Alcohol Depend.* 2020;214:108150. <https://doi.org/10.1016/j.drugalcdep.2020.108150>
- Dunbar M, Seelem R, Tucker J, et al. Correlates of Awareness and Use of Heated Tobacco Products in a Sample of US Young Adults in 2018–2019. *Nicotine Tob Res.* 2020;22(12):2178–2187. <https://doi.org/10.1093/ntr/ntaa007>
- Auer R, Concha-Lozano N, Jacot-Sadowski I, et al. Heat-Not-Burn Cigarettes: Smoke by Any Other Name. *JAMA Intern Med.* 2017;177(7):1050–1052. <https://doi.org/10.1001/jamainternmed.2017.1419>
- Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med.* 2013;368:341–350. <https://doi.org/10.1056/NEJMs1211128>
- Li J, Hui X, Fu J, et al. Electronic cigarettes versus nicotine-replacement therapy for smoking cessation: A systematic review and meta-analysis of randomized controlled trials. *Tob Induc Dis.* 2022;20:90. <https://doi.org/10.18332/tid/154075>
- Brown J, Beard E, Kotz D, et al. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction.* 2014;109(9):1531–1540. <https://doi.org/10.1111/add.12623>