REVIEW PAPER

UROLOGICAL ONCOLOGY

Alternative tobacco products use and its impact on urologic health – will the lesser evil still be evil? A commentary and review of literature

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Introduction Alternative tobacco products, including electronic cigarettes (e-cigarettes) and non-combustible tobacco products or heat-not-burn (HNB) products, are substitutes to conventional combustible cigarettes with the potential to impact urologic health, similar to traditional smoking. Most urologists, however, have limited knowledge of these products and are unfamiliar with their potential health implications. We conducted a review to assess the impact of e-cigarettes and HNB products on urologic health.

Material and methods A bibliographic search covering the period up to April, 2021 was conducted using MEDLINE®/PubMed® and Google Scholar. Articles were reviewed and categorized based on the potential impact on erectile dysfunction, semen quality, lower urinary tract symptoms, genitourinary malignancies, and smoking cessation. Data were extracted, analyzed and summarized.

Results Mature data on the long-term impact of e-cigarette and HNB product use on urologic health are lacking. E-cigarette and HNB vapors appear to contain decreased concentrations of chemicals responsible for erectile dysfunction compared to tobacco smoke but may play a role through endothelial damage. Use of e-cigarettes is associated with lower sperm counts. No definitive data has shown a link between e-cigarette or HNB product use and lower urinary tract symptoms. Multiple carcinogens including those specifically linked to bladder cancer have been identified in the urine of e-cigarette and HNB product users. Limited data suggest e-cigarettes may aid in smoking cessation.

Conclusions Urologists may benefit from understanding the urologic health concerns surrounding e-cigarettes and HNB product use and patients may benefit from being properly educated.

Key Words: heat-not-burn ‹› electronic cigarettes ‹› e-cigarettes ‹› combustible cigarettes

INTRODUCTION

Alternative tobacco products, including electronic cigarettes (e-cigarettes) and heat-not-burn (HNB) products, are a public health crisis with an exponential rise in their use [1, 2, 3]. Both e-cigarettes and HNB products are marketed as alternatives to conventional combustible cigarettes, but their health profiles are not well understood [4, 5]. Emerging data has recently highlighted the association of e-cigarette or HNB product use with several diseases well known to be linked with conventional smoking including nicotine dependence, pulmonary injury and cardiovascular disease, along with potential risks for malignancy [6–11]. Traditional cigarette smoking is causally associated with

a multitude of urologic diseases including erectile dysfunction, abnormal semen quality, and lower urinary tract symptoms, as well as kidney and bladder cancer. Developing research has begun to question if the use of e-cigarettes and HNB products may be associated with the same urologic diseases as the use of combustible cigarettes. Additionally, patients with urologic diseases may adopt e-cigarette or HNB product use as part of a perceived risk reduction strategy or cessation aid in those who smoke, further heightening the need to understand the urologic health implications of their use [12–15]. As e-cigarette or HNB product use has the potential to influence many urologic disease processes, the objective of this commentary and literature review to is provide the Urologist with an overview of these products and highlight their potential impact on urologic health.

E-cigarettes

Part of the challenge in assessing the potential health implications of e-cigarettes is the wide scope and variety of manufactured devices, along with the rapidly changing nomenclature. This is not only true of the products themselves, but also of the e-cigarette liquid. In general, the majority of e-cigarette devices have similar design characteristics and include 4 main components (Figure 1): 1) a cartridge or reservoir for the e-liquid, 2) a heating element or atomizer, 3) a lithium-ion battery, and 4) a mouthpiece [16, 17]. The cartridge holds a liquid solution (e-liquid) containing varying amounts of nicotine, flavorings, and other chemicals dissolved in carrier solvents such as propylene glycol and/or vegetable glycerin. The last two of the listed ingredients are generally recognized as safe for ingestion, but there is little evidence regarding their safety for long-term inhalation. The e-cigarette is designed to vaporize the e-liquid solution (called vaping) which then condenses into an aerosol for inhalation. By delivering nicotine through aerosolization rather than via combustion and traditional 'tobacco smoke', e-cigarettes lack many of the byproducts of traditional burning and produce fewer toxins. However, the additive and solvents of the e-liquid may form toxic and carcinogenic compounds when heated, such as nitrosamines, polycyclic aromatic hydrocarbons (e.g. pyrene, naphthalene, fluorene, phenanthrene), volatile organic compounds (e.g. acetaldehyde, acrylamide, acrolein, benzene, O-toluidine), and metals.

The design of e-cigarettes has evolved over time to include 1st, 2nd, and 3rd generation devices which vary in cartridge types and the ability to modify the voltage delivered to the heating coil. JUUL, a most commonly recognized 4th-generation product has gained popularity as it is frequently used among adolescents. The JUUL device (and its imitators) has an appearance similar to that of a USB drive. Rather than vaping, JUUL users are said to be 'JUULing'. Depending on the puff frequency and the e-liquid used, e-cigarettes users can get less, equal, or more nicotine than with traditional cigarette smoking. The amount of nicotine in one JUUL cartridge, or in about 200 puffs is roughly equal to the amount of nicotine in one pack of cigarettes.

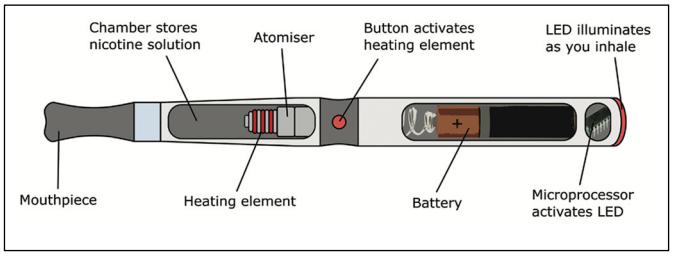

Figure 1. *Schematic of the electronic cigarette elements. Reproduced with permission from: Mathur A, Dempsey OJ. Electronic cigarettes: a brief update. JR Coll Physicians Edinb. 2018; 48: 346-351.*

Heat-not-burn products

Heat-not-burn (HNB) products, or non-combustible tobacco products, also known as heated tobacco products, apply heat from an electronically controlled device to various forms of tobacco. The device generates a nicotine-containing aerosol which is then inhaled [3]. The most important difference between HNB products and combustible cigarettes is that the heat applied to tobacco does not exceed a maximum operating temperature of 350°C (662°F) compared to the temperature of a burning cigarette of 800°C (1300°F). Theoretically this mechanism is intended to reduce concentrations or even avoid toxicants generated during traditional smoking. However, more research is needed to confirm these findings. The devices are designed to be similar to their combustible counterparts and replicate oral inhalation and exhalation, taste, rapid systemic delivery of nicotine, hand-to-mouth feel and throat hit sensations that are similar to smoking traditional cigarettes. When using HNB products, there is no smoke or odor as with traditional cigarettes and no ash is formed. There are different types of heated tobacco products in the marketplace. Some examples include products that use tobacco 'sticks' such as IQOS (I Quit Ordinary Smoking, by Phillip Morris) and glo (by British American

Tobacco) or products that use loose-leaf tobacco such as Pax or Ploom Tech. Importantly, for the Food and Drug Administration's (FDA) purposes, if a tobacco product meets the legal definition of a cigarette but the tobacco is not heated to a temperature high enough to cause combustion, the product would be currently categorized as a non-combusted cigarette and regulated as a cigarette. Up to date, of the above-mentioned products, the IQOS system has been authorized by the FDA to be marketed as a modified-risk tobacco product.
The IQOS, which is the most widely used HNB product, consists of two components with different functions (Figure 2). The first is a pen-like heater (holder) in which the tobacco stick ('HeatSticks') is inserted. The stick is then heated by means of an electrically controlled heating element and a charger, which recharges the heater after use. The charger stores sufficient energy for the use of approximately 20 tobacco sticks. The holder supplies heat through the heating blade for a fixed period of approximately 6 min and allows up to 14 puffs to be taken during that time. Each 'HeatStick' contains about the same amount of nicotine as one cigarette. The temperature of the heating blade is controlled and the energy supply to the blade is cut if its operating temperature exceeds 350°C. The aerosol and gases which are generated are composed of water, glycerin, nicotine and other compounds through evaporation/distillation processes. When the energy source is switched off, the temperature of the tobacco begins to decrease.
The tobacco stick differs from a cigarette since the tobacco is ground and reconstituted into sheets (termed cast-leaf) following the addition of water, glycerin, guar gum and cellulose fibers. These contain relatively smaller amounts of tobacco compared with regular cigarettes. Also, it contains two filters: a polymer-film filter to cool the aerosol and a low-density cellulose acetate mouthpiece filter to mimic the aspect of a cigarette. To operate the IQOS, the user inserts a tobacco stick into the holder and turns on the device by means of a switch. This initiates the heating of the tobacco via the heating blade inserted into the tobacco plug.
Glo resembles a small, very simple box mod. The device consists of a high-capacity power bank with a heater in the form of a barrel, into which tobacco sticks ('Neostiks') are inserted and heated from outside, not inside. The operation of this device is similar to other HNB products.

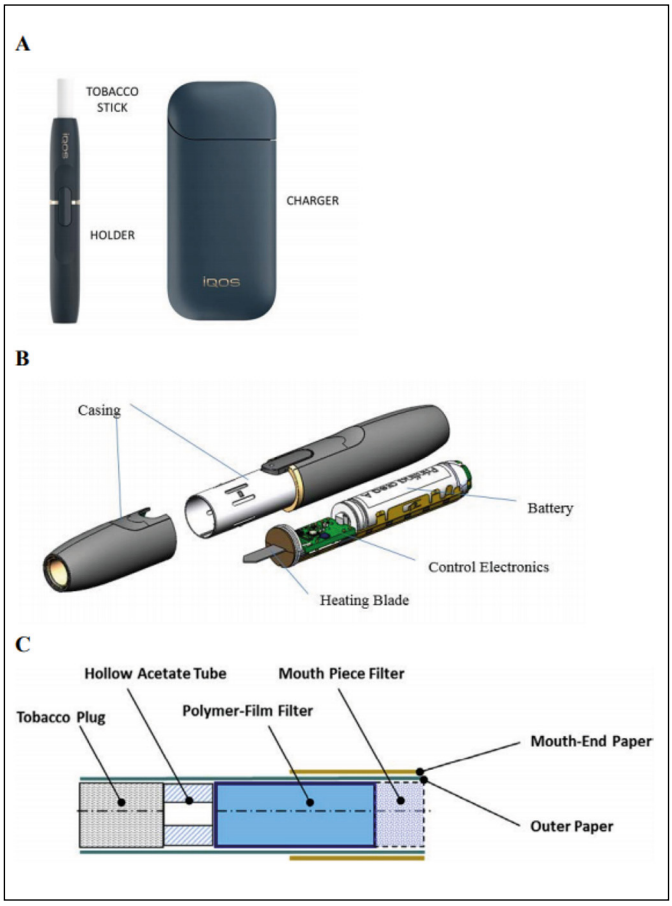

Figure 2. *The Tobacco Heating System (THS) components (A), a schematic exploded view of the Holder (B), and a schematic cross-section view of the Tobacco Stick (C). Reproduced with permission from MRTPA – THS Executive summary (https://www.fda.gov/media/105437/download).*

Potential impact of e-cigarette and heat-not-burn product use on urologic health

Erectile dysfunction

Smoking is a known risk factor for erectile dysfunction (ED) [18]. The exact mechanism of how the compounds of tobacco smoke cause deterioration of erectile function is yet not fully understood and most probably involves multiple factors. Interestingly, smoking has been proved to be a significant risk factor for ED even in young men and regardless of other vascular risk factors [19], indicating an independent and more direct role of smoking in the pathogenesis of ED. Preliminary studies have shown that exposure to e-cigarettes leads to vascular damage, albeit lower levels, than traditional cigarette use [20]. There is substantial evidence to claim that apart from the exacerbation of atherosclerotic damage to penile vessels, a major role of tobacco smoke in contributing to erectile dysfunction is the induction of oxidative stress, which leads to reduced bioavailability of nitric oxide (NO)

and thus to compromised erectile function [21]. It has been shown in several studies that smoking cessation may lead to some degree of improvement in erectile function, with young age, limited smoking history and lack of comorbidities yielding better outcomes [22]. As atherosclerotic lesions are irreversible in many cases [23], it may be the loss of oxidative stress induction that predominately contributes to the improvement in erectile function in patients who quit smoking. The current literature lacks data comparing the rates of erectile dysfunction between e-cigarettes or HNB products users and combustion cigarettes smokers or non-smokers, making it impossible to draw reliable conclusions in regards to the possible impact of these alternative tobacco products on erectile function. A recent systematic review concluded that data obtained from animal models suggest e-cigarette use affects erectile dysfunction [20]. It might be speculated that while the combustion cigarette smoke does contain the compounds responsible for inducing oxidative stress [24] and an HNB device expose its user to significantly lower concentrations of these chemicals [5], the HNB tobacco product users might be at decreased risk of ED compared to conventional smokers due to possible reduction in oxidative stress. However, nicotine itself (a known vasoconstrictor) has been reported to cause endothelial impairment due to an increase in oxidative stress [25], and impaired sexual and erectile function has been demonstrated in humans and animals in response to nicotine administration [26], which could make us consider any type of nicotine-replacement therapy, including e-cigarettes or HNB devices, potent of compromising erectile function, until proven otherwise. To conclude, while e-cigarette or HNB vapors appear to contain decreased concentrations of chemicals responsible for erectile dysfunction, still further research is needed before any definitive conclusion in regards to the risk of ED in these device users can be made.

Semen quality

There is large amount of evidence demonstrating the negative impact of tobacco smoking on semen quality. A meta-analysis of twenty available studies demonstrated that exposure to cigarette smoking was significantly associated with reduced sperm count, sperm motility and sperm morphology, with the negative effect being more pronounced in heavy smokers, suggesting a dose-dependent relationship [27]. The mechanism of how tobacco smoke exposure results in semen quality deterioration has not been fully understood up to date, with negative impact of cigarette smoke compounds on spermatogenesis [28], the oxidative stress [29] or alterations in serum testosterone levels [30] being suggested as possible explanations. Interestingly, nicotine itself has been shown to significantly decrease sperm motility and count in an animal study [31] and a study on humans demonstrated a significant and negative correlation of sperm motility to cotinine and trans-3'-hydroxycotinine seminal concentrations, both of which were observed to be increased in smokers [32]. The negative effect of tobacco smoke exposure on semen quality does not appear to be permanent, as the available evidence suggests that smoking cessation may lead to restoration of semen parameters [31, 33]. Up to date, no studies regarding the impact of HNB tobacco products on semen quality have been published in the literature. There is, however, some evidence in regards to e-cigarettes, as a recent cross-sectional study by Holmboe et al. demonstrated that the use of e-cigarettes was associated with significantly lower sperm counts, comparable to that of cigarette smokers [34]. Additionally, a recent systematic review found that preliminary data, obtained in animal models, suggest e-cigarette use impacts sperm parameters, though less than traditional cigarettes [20]. Whether the findings on e-cigarettes could be translated to HNB products remains an area requiring further investigation. Considering the abovementioned possible role of nicotine itself in the process of semen quality deterioration, it is complete smoking cessation that should be advised to a patient in terms of improving their semen parameters, until first studies on the use of HNB products in regards to semen quality are available.

Lower urinary tract symptoms

Evidence regarding tobacco smoking and lower urinary tract symptoms (LUTS) is very limited. While several studies demonstrated a negative effect of tobacco smoking on the degree of LUTS [35, 36], other authors published results suggesting a lack of such an association [35], and the available data have not been meta-analyzed up to date. The mechanism of this possible impact of tobacco smoke exposure on developing or exacerbating preexisting LUTS is yet unknown, and may be partially explained by augmented sympathetic nervous system response through activation of nicotine receptors [37]. A recent meta-analysis demonstrated no significant association between tobacco smoking and benign prostate hyperplasia risk [38], which may suggest a more complex mechanism underlying the impact of tobacco smoke exposure on the degree

of LUTS, possibly involving the link between smoking and chronic prostatic inflammation [39]. No evidence regarding such an association between the use of HNB products nor e-cigarettes has been published in the literature up to date. This, as well as the lack of strong data regarding the character of a possible impact of tobacco smoking on LUTS, with the mechanisms of such an impact still remaining unexplained, both make it premature to draw conclusions in regards to any possible relationship between smoking cessation or the use of HNB products or e-cigarettes and LUTS.

Malignancy

The cancer risk associated with the use of e-cigarettes or HNB products hypothetically would be expected to be less than tobacco cigarettes based on the rationale that e-cigarettes and HNB devices have a reduced burden of carcinogens delivered to the user and therefore less carcinogenicity. The etiology of cancers induced by environmental exposures is a complex, multistep process that generally takes years to develop but there are several biologically plausible pathways for which components of e-cigarettes and HNB devices could conceptually influence cancer development. Studying the potential impact of e-cigarettes or HNB device use on cancer development, however, is challenging. Many e-cigarette or HNB device users will be current or former combustible tobacco cigarette smokers, especially in the near term, and the effects of current and former smoking will be a challenging confounder to account for in observational studies. Additionally, given the time dedicated to epidemiological data generation (at least 20 to 40 years for cancer endpoints), alternative near term cancer endpoints and biomarkers may be the focus of current studies.

Both e-cigarettes and HNB devices produce a variety of chemical compounds during the heating process, many of which are the same toxicants and carcinogens found in combustible cigarette smoke. These substances are considered biomarkers of exposure and while they can be used as measures of exposure to harmful and potentially harmful constituents within alternative tobacco products, the degree of carcinogenicity of particular biomarkers of exposure may vary from slightly or even no carcinogenic to strongly carcinogenic. The subsequent metabolites or derivatives may, in some cases, be even more potent carcinogens than the original biomarkers, adding to the challenging nature of studying the urologic carcinogenic implications of e-cigarette or HNB use. For example, the biomarker of exposure produced by the device may be metabolized to a different compound in the blood or urine, and therefore the timing of specimen collection and individual metabolic properties can have a significant influence on detection.

Both e-cigarettes and HNB devices produce several biomarkers of exposure that are linked to bladder cancer and kidney cancer, including tobacco specific nitrosamines, polycyclic aromatic hydrocarbons, as well as volatile organic compounds (Table 1), albeit at lower levels than in combustible cigarettes [7, 40, 41, 42]. A total of 40 parent compounds and 4 metals have been identified in the urine of e-cigarette users: 12 in International Agency for Research (IARC) on Cancer Group 1 (Carcinogenic to humans), 4 in Group 2A (Probably carcinogenic to humans), 8 in Group 2B (Possibly carcinogenic to humans), 8 in Group 3 (Not classifiable as to its carcinogenicity to humans), none in Group 4 (Probably not carcinogenic to humans), and 10 not listed on the IARC monographs. Importantly, 6 carcinogens with a strong link to bladder cancer have been observed in the urine of e- cigarette users including pyrene, naphthalene, fluorene, phenanthrene, o-toluidine, and 2-naphthylamine), and 6 have a limited link (4 tobacco specific nitrosamines, lead, and chromium) [7]. Many of these similar carcinogenic compounds have been observed in the urine of HNB device users [3, 41, 43]. Whether or not the levels of exposure are high enough to contribute to human carcinogenesis remains to be determined. There is an increasing number of both in vitro and murine model studies investigating the various carcinogenic and mutagenic pathways and effects of exposure to the liquid used in e-cigarettes, the e-cigarette vapor, and HNB product smoke on different organ systems. Mice exposed to e-cigarette aerosols have been observed to sustain extensive DNA damage in lungs, heart, and bladder mucosa, diminished DNA repair in lungs, and later developed lung adenocarcinomas and bladder urothelial

Table 1. *Quantity of biomarkers of exposure in cigarettes, e-cigarettes, and heat-not-burn products*

Chemical class	Tobacco smoke	E-cigarette	Heat-not--burn
Tobacco specific nitrosamines	++++	+	+++
Nicotine	++++	++++	+++
Polycyclic aromatic hydrocarbons	++++	+	+++
Volatile organic compounds	+++	+	++
Metals	+++	++	++

E-cigarette – electronic cigarette

hyperplasia [11, 44]. In vitro studies of urine from e-cigarette aerosol-exposed rats have demonstrated an increase in the mutagenicity of urine compared to non-exposed rats [45]. The same researchers have found a fourfold increase in the levels of 8-OHdG in rats exposed to e-cigarette aerosol [45]. 8-OHdG is a widely used, but nonspecific, oxidative stress biomarker of oxidative damage to DNA and often considered as an intermediate biomarker of carcinogenic potential. Additional work has noted e-cigarettes have a booster effect on phase-I carcinogen bioactivating enzymes in a rate lung model [45]. Similarly, HNB devices have been shown to induce oxidative stress response in primary rat alveolar epithelial cells which play a role in the pathogenesis of lung cancer [46]. E-cigarette aerosol has been observed to promote breast carcinoma progression and lung metastasis in vitro through macrophage-tumor cells crosstalk and the role of CCL5 and VCAM-1 [47]. Interestingly, one of the proposed mechanisms of increased cancer risk is through the increased activation of the sympathoadrenal system induced by inhalation of nicotine, the primary component of e-cigarettes. Neuroscientific and oncological research has highlighted the role of the nervous system in cancer, as some cancers seem to be more sensitive to the stimulatory effect of the sympathoadrenal, such as prostate cancer [48]. Estimates of health risks associated with e-cigarettes and HNB products have demonstrated that the mean lifetime cancer risk values were decreased by more than one order of magnitude when comparing HNB device and e-cigarettes to commercial cigarettes [49]. These studies, taken together, underscore that the long-term urologic malignancy implications of exposure to e-cigarette or HNB device users are unknown and will require additional translational investigation and long-term population-level follow-up.

Is there a role for e-cigarettes and heat-not-burn products in a smoking cessation strategy?

The data remain limited on the efficacy of e-cigarettes or HNB products to facilitate smoking cessation. The Cochrane Database review published in 2016 evaluated the safety and effect of using e-cigarettes to help people who smoke achieve long-term smoking abstinence. Authors concluded that there was some weak data showing that e-cigarettes help smokers to stop smoking in the long-term compared with placebo e-cigarettes [50]. In the update of Cochrane analysis, the authors concluded that based on moderate-certainty evidence, e-cigarettes with nicotine increase quit rates compared to e-cigarettes without nicotine and compared to nicotine replacement therapy. Also, e-cigarettes were found to be relatively safe, but only short-term observation studies were available. However, only 4 of the 50 studies that were included in the review were rated as low-risk of bias and 37 of them as high [50]. Additional systematic reviews and meta-analyses have found conflicting results including that e-cigarettes were associated with significantly less quitting among smokers [13] and that the use of e-cigarettes was associated with smoking cessation and reduction [51]. Hajek et al. reported the results of a multicenter, pragmatic, randomized trial of e-cigarettes, as compared with nicotine-replacement therapy which showed e-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, both products being accompanied by behavioral support [52]. An Updated Evidence Report and Systematic Review for the US Preventive Services Task Force (USPSTF) noted five trials (n = 3117) reported inconsistent findings on the effectiveness of electronic cigarettes on smoking cessation at 6 to 12 months among smokers when compared with placebo or nicotine replacement therapy, and none suggested higher rates of serious adverse events [53]. The newest USPSTF statement concludes that the evidence on the use of e-cigarettes for tobacco smoking cessation in adults is insufficient, and the balance of benefits and harms cannot be determined. The USPSTF identified the lack of well-designed, randomized clinical trials on e-cigarettes that report smoking abstinence or adverse events as a critical gap in the evidence [54].

Smoking is a national epidemic in Poland and is the leading cause of preventable death, being responsible for approximately 70,000 deaths annually [55]. In Poland alone, smokers now represent close to 29% of the adult population, or approximately nine million individuals, while the economic cost of smoking in Poland is significant. The costs of smoking-attributable productivity loss within a year in Poland amount to about 2.6% of Polish annual gross domestic product (GDP), which is more than in Germany, Sweden, or the USA [56]. Two repeated cross-sectional nationwide surveys studies conducted in Poland – WOBASZ and WOBASZ II observed that the most common reason for quitting smoking among smokers in both studies for men and women alike was the fear of illness [57]. A recent cross-sectional study of a representative nationwide sample of 1011 Poles highlighted that 4.0% of participants had ever used e-cigarettes and 1.4% were current e-cigarette users [58]. Given the relatively recent arrival of HNB products on the market, heated tobacco product use was endorsed

by only 0.4% of participants. Among adolescents in Poland, the prevalence of dual users increased from 4% in 2010–2011 to 24% in 2015–2016 [59]. Smokers may adopt e-cigarette or HNB product use as part of a perceived risk reduction strategy or cessation aid. This strategy aims to curb combustible cigarette smoking by encouraging smokers to switch to potentially lower-risk tobacco products. However, this approach appears to have limited success and may potentially promote dual use [12–15].

Guidelines on e-cigarette and heat-not-burn products use

The World Health Organization (WHO) highlights that in order to help tobacco users quit smoking and to strengthen global tobacco control, governments need to scale up policies and interventions that are known to work. They underscore that tried and tested interventions, such as brief advice from health professionals, national toll-free quit lines, and cessation interventions delivered via mobile text messaging is recommended, rather than alternative tobacco products. However, not all organizations have this same stance. The Center for Disease Control (CDC) states that e-cigarettes have the potential to benefit adult smokers who are not pregnant if used as a complete substitute for regular cigarettes and other smoked tobacco products. However, e-cigarettes are not FDA approved as a smoking cessation device. The National Institute for Health and Care Excellence (NICE) in the United Kingdom states that among smokers who are interested in smoking cessation, many people have found e-cigarettes helpful to quit and emphasizes the evidence suggests that e cigarettes are substantially less harmful to health than smoking but are not risk-free, and evidence in this area is evolving. The European Public Health Association concluded that overall, e-cigarettes may help some smokers quit but, for most, e-cigarettes depress quitting.

Few organizations have established statements regarding the use of HNB products given their relatively recent arrival and limited research. The WHO does comment that all forms of tobacco use are harmful, including HNB tobacco products. The CDC clearly states heated tobacco products have not been scientifically shown to help smokers quit.

CONCLUSIONS

The use of e-cigarettes and HNB products use are on an upward trend and their impact on urologic health may be significant. Long-term implications on erectile dysfunction, semen parameters, lower urinary tract symptoms, and urologic malignancy are yet not well recognized, but considering the similarities of non-combustible nicotine products to traditional tobacco smoke, their potential impact is concerning. Further studies on the safety of e-cigarettes and HNB products in terms of urologic health is necessary. Urologists should be aware of these concerns and work to properly educate their patients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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