The role of heat-not-burn, snus and other nicotine-containing products as interventions for epileptic patients who take phenytoin and smoke cigarettes

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ABSTRACT

Background: Cigarette smoke increases the metabolism of phenytoin, a widely used anti-epileptic agent, by inducing cytochrome P450 enzymes in the liver. Therefore, cigarette smoke may reduce the clinical effect of phenytoin. Switching from cigarettes to smoke-free products (e.g., heat-not-burn, snus and e-cigarettes) is likely to have an impact on phenytoin metabolism. The absence of tobacco combustion in these smoke-free products reduces the production of the chemicals that induce the metabolism of phenytoin.

Objectives: The primary objective was to determine whether smoke-free products have a role to play in epileptic patients who take phenytoin and continue to smoke cigarettes. The secondary objectives were to assess: (1) the influence of cigarette smoke on phenytoin metabolism including the metabolic pathways involved, (2) the influence of nicotine on phenytoin metabolism including the metabolic pathways involved, if any, and (3) the influence of nicotine on epilepsy in humans, if any.

Methods: The literature review was conducted in 2019 and 2020 using a structured search to identify relevant articles. The potential mechanisms underlying the effects of cigarette smoke and nicotine on phenytoin metabolism and the pathways for phenytoin metabolism were evaluated to determine overlapping mechanisms/pathways. The key methodological deficiencies in the studies were recorded, where applicable.

Results: Thirty-five studies were reviewed. The literature showed that cigarette smoke influenced the metabolism of phenytoin by increasing the maximum metabolism rate of phenytoin by an average of 16% in humans. Cigarette smoke is known to contain several polycyclic aromatic hydrocarbons (PAHs), which can lead to faster elimination of numerous medicines, including phenytoin. There is no literature assessing the direct influence of nicotine on phenytoin metabolism in humans and animals. The metabolic pathways of phenytoin and nicotine do not overlap indicating that nicotine does not influence the metabolism of phenytoin. Hence, complete switching to smoke-free products with similar nicotine concentrations to cigarettes, may reduce the influence smoking has on phenytoin metabolism in epileptic patients who take phenytoin and smoke. There was also no evidence to demonstrate that nicotine has the potential to trigger epilepsy in humans.

Conclusion: The literature showed that the increase in metabolic rate of phenytoin due to tobacco smoke is probably attributable to PAHs and not nicotine. The similar nicotine content between smoke-free products and cigarettes and the reduced levels of PAHs in smoke-free products indicate that there is a role for smoke-free products in epileptic patients who take phenytoin and smoke.

1. Introduction

Cigarette smoke has been shown to influence drug metabolism. The harmful and potentially harmful constituents (HPHCs) in smoke may interact with medicines via pharmacokinetic (mostly enzyme-induction) and pharmacodynamic (often nicotine-mediated) mechanisms [1,2].

Phenytoin is a widely used anti-epileptic medicine. It was chosen as an appropriate example for this evaluation considering that smoke was shown to influence phenytoin’s maximum metabolic rate (Vm) [3]. In addition, phenytoin’s pharmacokinetics is complicated by the nonlinearity of the dose-response relationship, which is a consequence of capacity-limited metabolism [4]. Hence, the influence of smoke on phenytoin metabolism may be clinically significant due to large fluctuations in serum phenytoin concentrations. Therefore, individualized
therapy with phenytoin is optimally required. An understanding of how cigarette smoke may influence dosage requirements is particularly important for medicines such as phenytoin.

As cigarette smoke influences the metabolism of phenytoin [3], it can result in lower serum phenytoin concentrations, which may cause a suboptimal therapeutic effect resulting in reduced epilepsy control. The influence of cigarette smoke on phenytoin metabolism should be considered in assessing responses to phenytoin therapy. Similarly, the influence of alternatives to cigarette smoking such as the use of heat-not-burn (HNB), snus, e-cigarettes and other nicotine-containing products should be considered. These products will be referred to collectively as ‘smoke-free products’ for the purpose of this publication. The absence of tobacco combustion in smoke-free products can reduce the influence of smoke on phenytoin metabolism and, if so, patients should be advised to have their dose of phenytoin reassessed when they switch from an induced metabolic state caused by cigarette smoke to smoke-free products.

As an example, the HNB technology heats tobacco without producing combustion, which reduces the production of HPHCs that are formed in cigarette smoke. The FDA (2018) [5] reported that the HPHCs were 54–99.9% lower in the aerosol generated by the HNB product that was the subject of this application than in the smoke of cigarettes due to absence of combustion. In the same analysis, the FDA (2018) [5] reported a greater than 90% reduction in benzo(a)pyrene, a polycyclic aromatic hydrocarbon (PAH). Similarly, it was shown that the levels of 3-OH-B[α]P, a metabolite of inhaled benzo(a)pyrene, had decreased from the baseline by approximately 65–71% and 71–77% when switching from cigarettes to a HNB product or smoking abstinence, respectively [6]. Due to the reduction in the levels of HPHCs, including PAHs in the HNB technology, a reduced influence on the metabolism of phenytoin by the cytochrome P450 enzymes in the liver is expected. Other nicotine-containing products, e.g. snus and nicotine replacement therapy, where no combustion of tobacco occurs are expected to have a similar effect.

The objective of this study was to determine whether smoke-free products have a role to play in patients who take phenytoin and smoke cigarettes.

Cigarette smoking is harmful and the best approach to reduce the risk of associated disease is smoking cessation. In this context, scientifically substantiated smoke-free products may be a better option than continued smoking for those adult smokers who choose not to quit smoking.

1.1. Objectives

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2. Methods

A structured literature search was conducted in 2019 and 2020 to achieve the objectives listed above and extended to include articles where smoking influenced drug metabolism and drug interactions in general. Thirty-five (35) publications were identified for review.

Electronic databases (Pubmed / MEDLINE, ScienceDirect, Google Scholar and Cochrane Library) were searched multiple times in 2019 and 2020.

The search included English-language articles and included the following as key search terms:

‘Smoke/Smoking’ AND ‘phenytoin metabolism’.

‘Nicotine’ AND ‘phenytoin interactions’.

‘Nicotine’ AND ‘phenytoin metabolism’.

‘Smoke/Smoking’ AND ‘drug metabolism’.

‘Smoke/Smoking’ AND ‘drug interactions’.

‘Nicotine’ AND ‘drug metabolism’.

‘Nicotine’ AND ‘drug interactions’.

‘Nicotine’ AND ‘epilepsy’.

‘phenytoin metabolism’.

Hand searches of articles related to the above search criteria were conducted. The literature is likely to be representative of the published information in this area.

Titles and abstracts were screened to determine whether full-text articles should be retrieved and reviewed. Eligibility criteria included subjects (adults and animals), language (English), and document type (journal articles and books). The studies were assessed using published scientific criteria. The key methodological deficiencies in the studies were recorded, where applicable. Conference abstracts were excluded as these provide insufficient detail to judge the reporting quality of studies.

The potential mechanisms underlying the effects of cigarette smoke and nicotine on phenytoin metabolism and the pathways for phenytoin metabolism were evaluated to determine overlapping mechanisms/ pathways.

3. Results

3.1. Influence of smoking on phenytoin metabolism

Cigarette smoke has been shown to influence the metabolism of phenytoin [3]. The study investigated the influence of smoke among other covariates on the population pharmacokinetic parameters of phenytoin in adult epileptic patients in the Western Cape, South Africa. The study population comprised 332 black and colored epileptic patients. The influence of cigarette smoke on Vm of phenytoin was determined using nonlinear mixed-effects modeling (NONMEM). The parameter model describing the influence of smoke on Vm was tested using the Michaelis-Menten, and the parallel Michaelis-Menten and first-order elimination models, to which 853 steady-state dose-to-serum phenytoin concentration pairs were fitted. The scaling factor for smoke was 1,16 which implied that smoke increased the Vm of phenytoin in the liver by 16% (Fig. 1) [3]. Cigarette smoke had the highest impact relative to the patient factors (race, age, gender, mild-to-moderate alcohol

$$CP_{ss} = \frac{1}{2} \left[ \frac{Vm}{Cl} + Km - \frac{R}{Cl} \right] - \sqrt{\frac{Vm}{Cl} + Km - \frac{R}{Cl} \left( \frac{R}{Cl} \right)^2 + \frac{4R.Km}{Cl}}$$

$$Vm = (\beta_1 \cdot WT \cdot \beta_2)RACE \cdot SMK \cdot AGE + \eta_1$$

$$Km = \beta_3 + \eta_2$$

$$Cl = \beta_4 + \eta_3$$

where RACE = 1 if coloured, otherwise = 1

SMK = 1 if smoker, otherwise = 1

AGE = 1 if ≥ 65 years, otherwise = 1

Fig. 1. Parallel Michaelis-Menten and first-order elimination model. Cp:ss: steady-state serum phenytoin concentration (ng/l); Vm: maximum metabolic rate (mg/day); Km: Michaelis-Menten constant (mg/l); R: dosing rate (mg/day); Cl: first-order (linear) clearance for phenytoin (l/day); WT: body weight (kg); RACE: black, colored or malay; SMK: smoking status – smoker or non-smoker; R: exponential (error) model, $\beta_1 = 3.86, \beta_2 = 7.45, \beta_3 = 112.0, \beta_4 = 1.10, \eta_1 = -1.16, \eta_2 = -2.31, \eta_3 = 0.88$. Reproduced from reference [3].
intake, body surface area) that were studied, excluding weight on metabolic rate of phenytoin. The results indicated that smoke significantly influenced Vm \((p < 0.05)\) [3,7]. In this population 49.7% of patients smoked cigarettes. In addition, being colored (the largest population group in the Western Cape) had a significant effect, i.e., a 10% increase in the metabolic rate of phenytoin (Fig. 1) [3]. In this study, 58.7% of colored patients smoked [8]. The two factors combined (being a smoker and colored) may have an additive effect on the metabolic rate of phenytoin. This knowledge could benefit epileptic patients who could be under-dosed due to smoking and have sub-therapeutic serum phenytoin concentrations due to cytochrome P450 enzyme induction.

The study also indicated that when smokers were separated into those who smoked less than 10 cigarettes and those who smoked 10 cigarettes or more per day, there was no difference in the fit of the model to the data. Similarly, when smokers were separated into those who smoked less than 20 cigarettes and those who smoked 20 cigarettes or more per day, there was no difference in the fit of the model to the data. Accordingly, patients could be categorized as smokers or non-smokers [3]. This implied that smoking a few cigarettes per day is likely to have an impact on phenytoin pharmacokinetics. Hence, smoking should be discouraged.

Besides the study of Valodia et al. [3], other studies [9,10] have reported on the effect of smoking on serum phenytoin concentrations but not on Vm. Serum phenytoin concentrations do not directly relate to Vm due to differences in protein binding, etc. Unlike the study of Valodia et al. [3], other studies involved a small number of patients, a limited number of serum phenytoin concentrations, a combination of antiepileptic medicines, and were retrospective in nature. Although the mean serum phenytoin concentrations and the mean concentration-dose ratios were lower in smokers than in non-smokers, the results did not show a statistically significant difference between these groups [9]. Gender appeared to be more important than smoking status in affecting phenytoin concentration-dose ratios. It is believed that the results of the study of Benetello et al. [9] should be interpreted with caution as sample sizes of 43 smokers and 45 non-smokers were too small for a reliable statistical comparison considering that the patients were on a combination of two or three antiepileptic medicines, and were retrospective in nature. Although the mean serum phenytoin concentrations and the mean concentration-dose ratios were lower in smokers than in non-smokers, the results did not show a statistically significant difference between these groups [9].

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To investigate whether nicotine affects the metabolism of phenytoin, studies were searched to determine whether there were any common enzymes influencing phenytoin metabolism or the effects on nicotine. There was no evidence that the pathways for phenytoin metabolism overlapped with those of nicotine in humans. Hence, it can be suggested that nicotine does not affect phenytoin metabolism.

In a single-blind randomized, cross-over two-arm study of 12 healthy smokers, Hukkanen et al. [16] assessed the effect of nicotine on CYP2A6 and CYP2E1 activity. While the number of subjects in this study was too small to make any definite conclusions, the authors reported that nicotine does not affect CYP2A6 and CYP2E1 activities. Similarly, in a follow-up publication Hukkanen et al. [17] concluded that nicotine has no role in the induction of CYP1A2 that is known to occur in smokers. As these enzymes are also involved in phenytoin metabolism it is highly likely that nicotine will also not influence phenytoin metabolism. There was no significant influence of nicotine administration on the pharmacokinetic parameters of caffeine, paraxanthine, theophylline and theobromine in humans [17]. Because caffeine metabolism to paraxanthine is a specific probe reaction for CYP1A2 [18], it can be concluded that CYP1A2 activity was not affected by nicotine dosing in humans. Therefore, the absence of nicotine effects on CYP1A2 would suggest that nicotine does not influence phenytoin metabolism.

**3.3. Nicotine and phenytoin metabolism**

To investigate whether nicotine affects the metabolism of phenytoin, studies were searched to determine whether there were any common enzymes influencing phenytoin metabolism or the effects on nicotine. There was no evidence that the pathways for phenytoin metabolism overlapped with those of nicotine in humans. Hence, it can be suggested that nicotine does not affect phenytoin metabolism.

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Studies in experimental animals have provided evidence for the role of nicotine in the induction of CYP1A1, CYP1A2 and CYP2E1 enzymes in the liver, lung, kidney, placenta and the brain [19–25]. In rats, nicotine induced the activity of several enzymes in the brain, including CYP2E1 and CYP2A1/2A2 [24], hence, it is unlikely that this effect will be of clinical significance for phenytoin metabolism in the liver. The discrepancy between human and animal studies may be explained by tissue and species-specific differences [17]. Based on the studies mentioned above, it can be assumed that the findings in experimental animals are not of clinical significance.

There appears to be no common enzymes that are influenced by...
nicotine and involved in the metabolism of phenytoin in humans.

It has been shown that cigarette smoke increased the metabolism of phenytoin [3] in humans. The current evidence indicates that nicotine does not have a direct effect on phenytoin metabolism. It can be assumed that the increase in phenytoin metabolism is due to the other constituents of smoke besides nicotine. Hence, nicotine replacement should not influence phenytoin metabolism. The lack of evidence of nicotine in phenytoin metabolism does not necessarily translate into a lack of effect of nicotine on phenytoin metabolism. This should be assessed in a study designed for this purpose in humans.

3.4. Nicotine and epilepsy

Nicotine binds to the nicotinic acetylcholine (nACh) receptor. Iha et al. [26] reported that nicotine elicited convulsive seizures by activating amygdalar neurons in mice and rats. They reported that α7nACh receptors played a role in inducing nicotine seizures. However, the functional role and mechanisms of α7nACh receptors in causing seizures and/or epilepsy are still unknown [26]. Further studies are required to evaluate the role and clinical relevance of the α7nACh receptor in the pathogenesis of epilepsy. It was reported the alpha3 [27], alpha5 [28, 29] and beta4 [29] subunits of nAChR may be involved in mediating seizures. These studies were conducted in mice and rats, hence, cannot be extrapolated to humans. Based on our literature review, there is no evidence to indicate that nicotine induces seizures in humans at concentrations used in cigarettes and smoke-free products. The lack of evidence does not necessarily translate into a lack of effect of nicotine in inducing seizures. This should be assessed in a study designed for this purpose in humans. The effect of nicotine or cigarette smoke on seizure risk in people with epilepsy is unknown [30] and has not been well reviewed [31]. Studies on the association between cigarette smoke and seizures or epilepsy are insufficient. However, epileptic patients who smoke, i.e., the patients referred to in this evaluation, are already consuming nicotine, and consequently, switching to a smoke-free product should not affect the influence of nicotine on seizures. It was reported that treatment with a nicotine patch can be an effective therapy in epileptic patients with nAChR gene variants. It was proposed that transdermal nicotine treatment in intractable epilepsy with known nAChR variants as an experimental therapy is considered. However, further clinical trials are needed to fully define therapeutic effects [32].

3.5. Role of smoke-free products in epileptic patients who take phenytoin and smoke cigarettes

The impact of smoking cigarettes on phenytoin pharmacokinetics places the potential effects of smoking cessation and smoke-free products into context. Patients should be regularly monitored regarding their smoking status and the appropriateness of their dose of phenytoin. The dose of phenytoin should be adjusted based on their smoking status.

Based on the evaluation of the literature, there may be a role for smoke-free products in epileptic patients who take phenytoin and refuse to quit smoking for the following reasons:

• As there is no combustion in smoke-free products, the production of PAHs will be reduced with no or minimal influence on phenytoin metabolism.

• Nicotine in unlikely to influence phenytoin metabolism.

• Nicotine is unlikely to trigger epilepsy in humans at concentrations used in smoke-free products.

The absence of combustion in smoke-free products may to some extent prevent the 16% increase in the metabolic rate of phenytoin induced by cigarette smoke, and hence, result in higher serum phenytoin levels, which may lead to improved epilepsy control. Smoke-free products contain small quantities of PAHs that could lower the impact on the metabolic rate of phenytoin to much less than 16%. The reduced metabolism of phenytoin resulting from smoke-free products may lead to phenytoin toxicity. Hence, close monitoring of the patient’s seizure frequency, serum phenytoin concentrations, and phenytoin toxicity are required.

4. Discussion

4.1. Role of smoke-free products

This evaluation indicated that smoking has a significant influence on the metabolic rate of phenytoin [3] in epileptic patients attending outpatient clinics. The chemicals of combustion in smoke, particularly the PAHs, induce the cytochrome P450 enzymes in the liver that metabolize phenytoin. It was reported that PAHs in tobacco smoke are responsible for the induction of CYP1A2 and possibly CYP2E1 [11], which are involved in the metabolism of phenytoin [13]. Cigarette smoke has been shown to induce CYP1A2 activity, which has been quantified to be 1.72-fold higher in heavy smokers (≥20 cigarettes per day) compared to non-smokers [33]. This may result in subclinical levels of phenytoin. Due to the absence of combustion in smoke-free products, a reduced amount of PAHs are produced, resulting in a decreased transcriptional activation of the genes [34] that are responsible for the metabolism of phenytoin. There is no evidence that nicotine triggers epilepsy [30] or induces cytochrome P450 microsomal enzyme activity [16,17] in the liver of humans that are relevant to phenytoin metabolism. Hence, smoke-free products (irrespective of their nicotine content) should be considered as alternative to cigarettes for epileptic patients taking phenytoin and who do not quit smoking. The literature was assessed to determine whether there were common enzymes involved in the metabolism of phenytoin and the effects elicited by nicotine, specifically whether nicotine influenced phenytoin metabolism. The absence of such an overlap of the metabolic pathways, indicates that the nicotine content of these smoke-free products will probably not affect the metabolic rate of phenytoin. This indicates that there is a role for smoke-free products in epileptic patients who take phenytoin and continue to smoke cigarettes.

The study by Valodia et al. [3] indicated that other factors such as weight, race, and age (65 years or older) play a role in phenytoin metabolism. Similar factors may also affect the metabolic rate of other medicines. Genetic polymorphisms of the CYP genes may contribute to extensive inter-individual variability in drug metabolism and are associated with altered induction of gene expression in smokers [11,35]. There are also marked ethnic differences in the distribution of CYP1A2 mutations, implying that different ethnic groups may respond differently to drug metabolism of smokers or those who stopped smoking [35]. This has been shown by Valodia et al. [3] (Fig. 1).

Most of the experimental work in humans and animals indicated that most pharmacokinetic interactions with smoking were the result of induction of hepatic cytochrome P450 enzymes [36]. This involves primarily CYP1A2 and drugs that are CYP1A2 substrates. Because the hepatic microsomal enzymes involved in phenytoin metabolism are not related to the nicotine component of tobacco [16,17], nicotine replacement should not influence phenytoin metabolism. In particular, nicotine replacement therapy does not influence CYP1A2 activity [37], an enzyme involved in phenytoin metabolism. CYP2B6 and CYP1A2 are well-known to be up-regulated in smokers [38]. Although the induction of CYP1A2 is mediated by the aryl hydrocarbon receptor, the molecular mechanisms of CYP2B6 induction by smoking remains to be fully elucidated [38].

The principles discussed above for phenytoin could be applied to other medicines. Similar to phenytoin, smoking has been shown to increase the metabolism of numerous other medicines such as theophylline, clozapine, fluvoxamine, olanzapine, imipramine, haloperidol, pentazocine, propranolol, flecainide, estradiol, methadone, irinotecan, etc. [2,34,37,39,40] by inducing a wide range of drug-metabolizing enzymes. Hence, there may be an impact in patients who smoke and
take medicines that are affected by smoking on switching to smoke-free products. If nicotine does not contribute to the increased metabolic rate for other medicines similar to phenytoin, then there is an important, and possibly, an unconsidered impact of smoke-free products in patients who take medicines that are affected by smoking.

The influence of smoke on the pharmacokinetics of many commonly used medicines renders smoking one of the primary sources of drug interactions. Cigarette smoke associated PAHs can induce key drug-metabolizing cytochrome P450 enzymes and isoforms of the glucuronyl transferase families [34]. Induction of these enzymes may lead to accelerated clearance of medicines [34], as with phenytoin, with resultant impact on efficacy in smokers compared with nonsmokers.

The potential for drug interactions after smoking cessation for patients who are taking phenytoin should be considered. After quitting smoking, an important consideration is how quickly the induction of hepatic cytochrome P450 enzymes dissipates. It was shown that cessation of cigarette smoke exposure or switching to HNB technology the upregulation of CYP1A2 observed with cigarette smoke reverted to fresh-air levels within five days [6]. Decreased activity of the hepatic cytochrome P450 enzymes after smoking cessation increases the risk of adverse drug reactions with phenytoin. Predicting the required dose reduction of phenytoin after smoking cessation is challenging. Due to the non-linear pharmacokinetics of phenytoin, small decrements of dose are recommended, which are guided by pharmacokinetic calculations and serum phenytoin concentrations. Careful consideration should be given to drug interactions on smoking cessation for numerous medicines. For other medicines, Faber and Fuhr [41] recommended a step-wise daily-dose reduction of approximately 10% until the fourth day after smoking cessation for drugs that are CYP1A2 substrates. When patients enter hospitals, they may be required to stop smoking abruptly if the hospital has a ‘no smoking’ policy. Such abrupt smoking cessation can affect the metabolism of drugs [39] and healthcare practitioners are urged to consider the clinical impact thereof.

The approach developed in this evaluation can be applied to other medicines where smoking can influence the metabolism of medicines. An intervention such as switching to smoke-free products may result in better control of diseases. If a switch to these products is recommended in a patient who continues to smoke cigarettes, then the clinical impact of this decision should be considered with reference to the influence of smoking on the clinical pharmacokinetics of the medicine. Patients who smoke, have recently quit smoking, or have switched to a smoke-free product should be screened for potential drug interactions due to the effect of smoke on drug metabolism.

5. Conclusion

The literature shows that the increase in the metabolic rate of phenytoin due to tobacco smoke is probably because of the PAHs and not the nicotine. Hence, there may be a role for smoke-free products in smokers who do not quit. This is due to the reduction in exposure to the PAHs resulting from tobacco combustion in cigarette smoke. This exposure reduction can also affect how the body metabolizes drugs, an important example being phenytoin, used by epileptic patients. Epileptic patients who smoke will be exposed to a similar concentration of nicotine if they switch to a smoke-free product. Care should be taken when smokers switch to smoke-free products as there might be a transient modification in nicotine exposure. The best option is for a smoker to quit smoking. It this is not possible, then the patient should consider a smoke-free product. Switching to a smoke-free product will likely result in lower levels of PAHs, which would be expected to lead to lower induction of hepatic microsomal enzymes and potentially, a slower rate of phenytoin metabolism. This may result in higher serum phenytoin concentrations, and hence, the dose of phenytoin may require adjustment. This is particularly important due to the narrow therapeutic index and the nonlinear pharmacokinetics of phenytoin.

It is hoped that this evaluation will encourage all healthcare practitioners to consider the influence of cigarette smoke on phenytoin metabolism and the clinical significance thereof. It is recommended that the role of smoke-free products, if any, is tested prospectively in a sample of epileptic patients taking phenytoin.

Declaration

The research was conducted by Praneet Valodia who currently serves as a healthcare consultant to numerous companies nationally and internationally.

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Declaration of Competing Interest

The author declares the following financial interests/personal relationships which may be considered as potential competing interests: The research was conducted by Praneet Valodia who currently serves as a healthcare consultant to numerous companies nationally and internationally. The research was conducted independently by the author and the views expressed in the article are the independent views of Praneet Valodia. The author had full editorial control over the article written. Philip Morris had no involvement in the design and conduct of the work.

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Conflicts of interest

Praneet Valodia serves as a consultant in scientific engagement to Philip Morris, South Africa.

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