Safety and Effectiveness of Electronic Cigarettes: A Narrative Review

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ABSTRACT

Objective: To current review the literature regarding safety and effectiveness of electronic cigarettes and to find out any contribution from Malaysia, regarding electronic cigarettes research field.

Design: To commendably face this new challenge, health care providers need to become more familiar with the existing literature. A narrative review studies conducted from 2004 to August 2014 through multiple electronic databases that available at the author’s institution library conducted by using the terms, safety, effectiveness, efficacy, chemical analysis of e-cigs, electronic cigarettes or electronic nicotine delivery system (ENDS). The databases searched only for full text papers published in English from 2004 to August 2014.

Methods: 48 original articles identified with help of multiple electronic databanks, that linked to aim title were selected. Nation wise contribution included, USA(16), UK(07), Italy(6), Greece(5), New Zealand(5), Switzerland(4), Canada, Australia, Poland, south Korea, Czech republic each 1. We did not found any article from Malaysia, this indicate us there is a necessity of electronic cigarettes studies on Malaysian population.

Conclusion: Due to limited studies with inadequate participants and short time exposure in some developed countries, e-cig cannot accomplish safe and effective in complete terms. In order to conclude firmly, still more research is needed globally in different population to look at its long-term safety and effectiveness particularly on cardiovascular diseases and on smoker’s health from different parts of the world.

KEY WORDS

Electronic cigarette, vaping, cessation, safety, effectiveness

INTRODUCTION

Electronic cigarettes (e-cigs) are gaining popularity and its use rises sharply every year. According to recent report prepared by world health organisation (WHO) stated that, till early 2014 there are 466 brands of e-cigs available in 7764 unique flavours(Zhu et al., 2014) and till the end of 2013 its sales reached to US$ 3 billion globally and it has been projected, the sales margins can rise up to US$10 by 2017(Herzog B et al., 2014). Worldwide there is no data for e-cig users (commonly called vapers). However data from some country suggested that, like North America, the European Union and republic of Korea, the e-cig users doubled among both adults and adolescents from 2008 to 2012(Grana et al., 2014). The spectacular success of e-cigs is a game-changing event in the field of tobacco control and even the tobacco industry has introduced their own brands.

Electronic cigarettes (e-cigs) are relatively new and the use is becoming a popular type of electronic nicotine delivery system (ENDS). It is a battery-powered device that looks like a cigarette but does not involve smoke and which enables users to inhale vaporized nicotine (WHO, 2009). The e-cigarette was developed with the goal of mimicking the action of smoking, including nicotine delivery, without the toxic effects of tobacco smoke which is responsible for nearly all of tobacco smoking's damaging effect (Cahn and Siegel, 2011; Siegel et al., 2011; Borland 2011; Foulds et al., 2011; and Wager et al., 2012). Further e-cigs generating vapours which visually look like smoke, that replace most of the bodily, civic and societal elements linked with smoking.

E-cigs transport to the lungs, a chemical mixture primarily consists of nicotine, propylene glycol, glycerine and few flavouring agents. They are often tactically look and feel like cigarettes. They have been promoted as substitutes to cigarettes and for usage in places where smoking is not tolerable since they do not generate smoke. They are also sometimes made to look like daily normal items such as pens, screw driver for people use so that, its appearance deprived of other people observing (WHO, 2009).

Concept of an E-cigarette was first patented in 1965 by Herbert A Gilbert (Gilbert, 1965). But then again the 21st century creation of e-cigarettes is recognized to Mr Hon Lik, a Chinese pharmacist (Kcancer, 2010). The device was first introduced to the Chinese domestic market in May 2004 as a support for smoking cessation. Then export began in 2005-2006, before an international patent in 2007.

A typical e-cigarette (Figure1) is made up of electronic vaporization system (contains heating coil), rechargeable batteries, electronic circuit and tanks to fill the e-juice to vaporize. The amount of nicotine in the e-juice may differ, the manufacturer's stated that the e-juice typically contain between 6 and 24 mg of nicotine (Goniewicz et al., 2012). Currently due to advancement of technology there are three categorizing of E-cigarettes available in the markets. Namely 1st generations (looks like traditional tobacco cigarettes), 1IInd generations (look like pens and screw drivers also called vape pens) or IIIrd Generations (also called advanced personal vaporizers (APVs or Modes). Each type gets gradually larger as you move up from I st Generations to IIIrd or APVs being the largest.

From 1st generation to third Generations, there is an improvement in...
features like improvement in battery life, use of different atomisers with various e-liquid filling capacities, advanced features such as variable voltage (VV) and/or variable wattage (VW), all these factors are important for better vapour productions and to increase the number of puffs.

There is rising curiosity as well as worry regarding e-cigs among cigarette smokers, entrepreneurs, health care professionals, policy managers and even tobacco industries. The World Health Organization has urged marketers of e-cigarettes to halt their unproved claims about the therapeutic benefits of using e-cigarettes and has indicated that there is no reliable scientific evidence to confirm the product's safety and efficacy (WHO, 2008). Certain believers of tobacco harm reduction have pointed to these products as feasible alternatives for cigarettes because they produce fewer toxins in the vapour delivered to the use (Cahn and Siegel, 2011; Siegel et al., 2011; Borland, 2011; Foulds et al., 2011; Wagener, 2012).

Cigarette smoking

Smoking is a chief source of adverse health effects in most countries globally. Smoking harms nearly every single organ of the body. Smoking origins many diseases and shrinks the health of smokers in over-all (WHO, 2003). Cigarette smoking is the single biggest avoidable cause of death and disability in developed countries. Smoking is now growing swiftly all over the world and is one of the biggest intimidations to current and future world health (WHO, 2003). For many smokers, leaving smoking is the chief imperative thing they can do to improve their health. Reassuring smoking cessation is one of the absolute cost effective things that physicians and other health professionals can do to improve health and prolong their patients' lives. The adverse health effects of smoking are wide, and have been comprehensively recognized. There is a substantial dose-response link with heavy smoking, duration of smoking, and premature use connected with higher risks of smoking related illness and mortality (Wilson et al., 2000).

Global Smoking statistics

Tobacco smoking is a global problem, affecting an approximately 1.3 billion people, projected to increase 1.6 billion by 2025 that create significant health problem and economic burden (Mathers & Loncar, 2006). According to the World Health Organization (WHO) tobacco use is presently accountable for the death of one in ten adults' worldwide. Presently 6 million deaths and this number of deaths due to smoking-related diseases are expected to reach 8.3 million by 2030 (WHO, 2008; US Department of Health and Human Services, 1990).

METHODS

A literature survey was done from March to August 2014 to identify published articles related to safety and effectiveness of electronic cigarettes. In this narrative review, we included studies that are potentially related to safety and effectiveness of Electronic cigarettes including chemical analysis, because it addresses the safety of device. Each article was revised by all authors and a consent meeting was summoned to ensure worth assurance of the manuscript.

The searched scheme involved nine most widely used electronic databases in health sciences, that included Medline, PubMed, Scopus, ISI Web of knowledge, science direct, Springer link, JSTOR, Proquest and Ebsco Host. The searched structure involved using Boolean operators for combination of the following terms: safety, effectiveness or efficacy, chemical analysis, electronic cigarettes, e-cigarettes, nicotine delivery system. These searches were accompanied by hand search of the reference lists in the reports identified. To ensure reports met the desired criteria, the lists of titles and abstracts from searches were scrutinized and where doubt remained, the whole paper was examined. The searched was limited to full papers articles published in English from 2004 to August 2014.

RESULTS

185 titles and abstracts were identified by all authors from above mention nine databanks and wherever possible by valuation of the reference lists. Among these Articles that includes, Erratum, book chapters, reviews, letter to editors, short communications, editorials notes, opinions, non-original data, not published in English language and duplicated citations were examined and excluded. Of these, 72 original articles that related to our topic were selected. The full text of 72 articles was retrieved and disseminated among all authors for further valuation. Among 72 documents all authors agreed that, 48 were suitable for inclusion in the review. Country wise contribution include, USA(16), UK(07), Italy(6), Greece(5), New Zealand(5), Switzerland(4), Canada, Australia, Poland, south Korean and Czech republic each 1. We did not found any article from Malaysia, this indicate us there is a need of electronic cigarettes studies on Malaysian population. The remaining manuscripts were excluded because their primary focus was not safety, effectiveness and chemical analysis of electronic cigarettes. So in the final review mainly 48 articles were selected. Although some other articles are also cited for background and context. The quorum flow chart for this review is shown in (Figure 2).

Studies on Effectiveness of E-Cigarette

Evidences strongly suggest that e-cigarettes may be effective in helping smokers to quit and preventing relapse, to our knowledge there have been few published studies to explain why this might be the case. Many health authorities refuse to say that, this product is beneficial for smoking cessation due to limited studies and the risks and benefits are still being calculating. The degree of effectiveness depends on what effect is being measured.

As per the Goniewicz et al., (2013) quitters perceive mainly four benefits these are, desire to smoke (craving), help to cut down cigarettes, help to quit entirely and eradicate the smell of stale smoke.
Safety and Effectiveness of Electronic Cigarettes

Some online surveys on e-cigarette users suggested that, e-cigarette helped them to quit or reduce smoking and vapers believe that it is less harmful than smoking (Etter, 2010; Etter & Bullen, 2011; Siegel et al., 2011; Foulds et al., 2011).

The trial by Bullen et al., 2010 on 40 naïve smokers measured the short-term effects of e-cigarettes on desire to smoke, withdrawal symp -
toms, acceptability, pharmacokinetic properties and adverse effects in a cross-over trial design. The results demonstrated that electronic ciga-
rettes deliver nicotine effectively, more rapidly than a nicotine inhaler, and the electronic cigarette use significantly reduced craving but less than with a regular cigarette (Bullen et al., 2010).

The Siegel et al., (2011) on 216 respondents, more than 70% male between 18 to 65 ages smoking for last 5-30 years, reported after 6 months of vaping, 31% of participants were no longer using tobacco cigarettes.

The clinical trial done by Caponnetto, P et al., (2013a) on 300 smokers in a randomized clinical trial (RCT) with no intention to quit, performed the efficiency and safety of an electronic cigarette (ELCAT), have found out smoking reduction was documented in 22.3% and 10.3% at week-12 and week-52 respectively. Complete abstinence from tobacco smoking was documented in 10.7% and 8.7% at week-12 and week-52 respectively. Declines in cig/day use and expired carbon monoxide (eCO) levels were observed and a substantial decrease was found in the adverse events as well. In another study by same author on 14 chronic schizophrenic smokers reported similar reductions in cigarette con-
sumption and abstinence after a yearlong trial by using e-cigs (Caponnetto et al., 2013b). The clinical trial done by Polosa, R et al., (2011) in a 6 month pilot study on 40 regular smokers with no desire to quit, reported a six-month prevalence smoking cessation rate of 22.5%. An additional 32.5% of smokers reduced their cigarette consumption by at least 50% by using e-cigarettes. The Polosa et al continued the trial in a naturalistic settings, have found out smoking reduction was documented in 50% and 24% of cig/day after 6 months was shown in 27.5% participants with a median of 24 cig/day use at baseline decreasing significantly to 4 cig/day (p = 0.003).

Smoking abstinence was reported in 12.5% participants while combined 50% reduction and smoking abstinence was observed in 40% par-
ticipants in two years (Polosa, R et al., 2013).

The trial by Dawkins et al., 2012 in 86 smokers, examined whether the e-cigarette can reduce desire to smoke and abstinence-related with-
drawal symptoms among three groups during 0, 5, 20 minutes period after vaping ad libitum for 5minutes. It was found that the electronic cigarette can reduce desire to smoke and nicotine withdrawal symptoms 20 min after its use. In another study by same author, on 1347 partici-
pants from 33 countries (> 70% European) online survey reported that, e-cig are mostly used for smoking cessation, but need a longer duration than nicotine replacement therapies (Dawkins et al., 2013).

The survey conducted by Goniewicz et al., (2013) on 179 respondents reported that 72% of users believed that e-cigs were beneficial in reducing toxic cravings and withdrawal symptoms while 92% declared that the devices had reduced the number of conventional cigarettes they smoked. Indeed, in the same survey, 96% of former smokers claimed that e-cigarettes had helped them quit, and 79% reported a fear that if they stopped using them they would start smoking again.

In study done by Barbeau et al.,(2013) on 11 participants ages between 18-64 in a focus group discussion posing open ended ques-
tions, revealed that, vaping was more successful in maintaining cigarette abstinence than FDA approved NRT therapies due to retention of behavioural and social element of smoking dependence.

Farsalinos et al., (2013) recruited 111 participants more than 84% male smoked smoked before at least 20 30 cigs/day, who had complete-
ly substituted conventional cigarette with e-cig for last one month shown, e-cig with high nicotine content were more successful in the smoking abstinence process.

Kralikova et al., (2013) taken interview of 2012 participants on the street of 17 cities of Czech republic, identified that about 20% of smok-
ers who tried e-cigs go on to become regular e-cig users (Kralikova et al., 2013).

Pokhrel et al., (2013 ) in a cross sectional study survey on Hawaiian islands on 1567 participants shown, smokers who tried e-cigs appear to be more serious about smoking cessation and treat e-cig as valid alternative to FDA approved nicotine replacement therapies.

A randomized controlled trial on large number of participant done by Bullen et al., (2013) to verify safety and effectiveness of e-cigs among 657 people shows that e-cigs, with or without nicotine, were modestly effective at helping smokers to quit, with similar abstinence rate achieved with nicotine patches. However, the study was underpow-
ered to conclude superiority of nicotine over nicotine patches (Bullen et al., 2013).

A recently worldwide survey of more than 19,000 consumers by farsalinos et al., (2014) on characteristics, perceived side effects and bene-
fits of electronic cigarette use reported, E-cigs were mostly used to avoid the harm associated with smoking and it is effective in highly-de-
pendent smokers and are used as long-term substitutes for smoking. The study also stated 57.9% participants faced at least one symptoms and the most common side effect were dry mouth and sore throat (38.9%).

A new recent cross sectional population study on 5863 adults to quit smoking with smoking aids such as E-cig, nicotine replacement therapy (NRT) and deprived of smoking aid for smoking cessation, were select-
ed in a real world settings without professional support. Among smok-
ers, 12.5% more likely to report for quit smoking were E-cig users com-
pared to NRT and no aid cessation users respectively (Brown et al.,2014).

An outline of the studies involving effectiveness of e-cigs, summa-
rized in the Table 1

Studies on E-Cigarettes Safety

A draft review by the WHO’s Tobacco Regulatory Group in 2009 notes that the extent of nicotine uptake and the safety of e-cigarettes have yet to be fully established. Most of the safety concerns regarding electronic cigarettes relate to the absence of appropriate product regulation and inconsistencies in quality control (WHO 2009).

The study done by Eissenberg (2010) on 16 smokers, naïve to e-cig-
arettes were cycled through the four device groups revealed that, smok-
ing but not vaping , notably increase nicotine and heart rate (Eissenberg, T.2010).

The trails done by vansickel et al., (2010) in above correlated situa-
tion, reported similar results. The key findings were, nicotine, expired carbon monoxide and heart rate all increased after smoking, but not vap-
ing, but later in 2013 Vansickel and Eissenberg study on 8 experienced E-cig users reported that, both smoking and vaping induced similar con-
comitant increases in heart rate and blood levels of nicotine (vansickel et al., 2013).

The results reported by Etter and Bullen (2011) on 31 respondents of e-cigarettes users from different countries after vaping ad libitum but abstained from cigarettes and NRTs for 48hrs. The study shown vaping and smoking induce similar increases in salivary cotinine levels than conventional cigarettes.

Czogala et al., (2012) have done comparison study on hemodynam-
ic parameters (Systolic and diastolic pressure, pulse and heart rate) in smokers and vapers on 42 subjects. The study shown that vaping e-ciga-
Table 1. Summary of studies involved in effectiveness of Electronic Cigarettes.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Patient sample size</th>
<th>Clinical outcomes and key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullen et al., (2010)</td>
<td>RCT, four groups comparison effect E-cig with or without nicotine, tob cigarette &amp; Nicorette nicotine inhaler</td>
<td>40 adult naïve dependent smokers (Average age (mean ± SD): 47.6 ± 12.4) with or without nicotine, 10% daily smokers</td>
<td>Tobacco cigarette effectively remove craving and withdrawal symptoms. E-cig with nicotine and nicotine inhaler have similar effect greater than e-cig without nicotine.</td>
</tr>
<tr>
<td>Ettet (2010).</td>
<td>Online French survey</td>
<td>81 participants, between 19-65, 63% former smokers 23% daily smokers 13% occasional smokers from different country</td>
<td>E-cigarette helped to quit smoking</td>
</tr>
<tr>
<td>Ettet and Bullen, (2011)</td>
<td>Internet survey</td>
<td>3587 respondents, between 31-52, 70% former smokers, 19% daily smokers 11% occasional smokers</td>
<td>Respondent reported E-cigs helped them to quit or decreased smoking and vaping less toxic than smoking.</td>
</tr>
<tr>
<td>Foulds et al., (2011).</td>
<td>Survey at e-cig enthusiasm convention (interview)</td>
<td>104 respondents mean between 34 ± 9, 78% former smokers, 19% daily smokers</td>
<td>E-cig helped them to quit or decreased cigarette consumption and vaping less harmful than smoking.</td>
</tr>
<tr>
<td>Siegel et al., (2011).</td>
<td>Online survey</td>
<td>216 participants ages 18-65 ± years, smokers for 5-30 + years</td>
<td>After 6 months of E-cig 31% of participants were no longer using tobacco cigarettes.</td>
</tr>
<tr>
<td>Bullen et al., (2013)</td>
<td>Randomized controlled trail on 657 respondents.</td>
<td>E-cig group(n = 289) age 44 ± 13 years, nicotine patch group(n = 295) age 40 ± 13 years e-cig placebo group (n = 73), age 43 ± 12 years</td>
<td>E-cig with or without nicotine were effective at helping smokers to quit smoking as nicotine patches</td>
</tr>
<tr>
<td>Barbeau et al., (2013).</td>
<td>Focus group discussions facing open ended questions</td>
<td>Nine men and two women, between 18-64 years</td>
<td>Participants reported E-cig is more helpful than FDA approved nicotine replacement therapies due to retention of behavioral and social components of smoking addiction</td>
</tr>
<tr>
<td>Caponnetto et al., (2013a).</td>
<td>RCT: prospective 12-month randomized, controlled trial.</td>
<td>300 smokers no intention to quit, mean age 44 ± 13 years, 63% male and smoke at least 15-25 cigarettes/day</td>
<td>The use of e-cig with or without nicotine , decreased cigarette consumption and elicited tobacco abstinence</td>
</tr>
<tr>
<td>Caponnetto et al., (2013b).</td>
<td>Chronic schizophrenic patients observed for 12 months</td>
<td>14 Chronic schizophrenic patients mean age 45±13 years and consumed 20-35 cigarette /day</td>
<td>E-cig use decreased cigarette consumption without causing any significant side effects in schizophrenic patients</td>
</tr>
<tr>
<td>Dawkins et al., (2013).</td>
<td>Online survey</td>
<td>1347 participants, mean age 43 years, Respondents from 33 countries.</td>
<td>E-cig mainly used to quit smoking .study also reported there is very little evidence that E-cig is not the gateway for nonsmokers.</td>
</tr>
<tr>
<td>Farsalinos et al., (2013).</td>
<td>Smokers substituted with e-cig for at least 1 month</td>
<td>111 participants, average 37 ± 6 years, smoked 20-30 cig/day from Greece.</td>
<td>E-cig with higher nicotine useful in quit smoking compare to less or no nicotine.</td>
</tr>
<tr>
<td>Goniewicz et al., (2013a).</td>
<td>Internet survey</td>
<td>179 respondents from Poland</td>
<td>E-cig mainly used to quit smoking with less harm effects.</td>
</tr>
<tr>
<td>Polosa et al., (2013).</td>
<td>A 24 month observational study</td>
<td>40 regular smokers, 26 males, 14 females; mean ± SD age of 42.9 ± 8.8 years Regular smokers (mean ± SD): 34.9 ± 14.7 pack/years</td>
<td>After Long term e-cig use decreased in &gt; 50% consumption of traditional cigarette along with 12.5% of abstinence rate as verified eCO(exhaled carbon monoxide).</td>
</tr>
<tr>
<td>Polosa et al., (2011).</td>
<td>A prospective 6 month pilot study</td>
<td>40 regular smokers, 26 males, 14 females; mean ± SD age of 42.9 ± 8.8 years Regular smokers (mean ± SD): 34.9 ± 14.7 pack/years</td>
<td>After 6 month , E-cig decreased 50 to 80% consumption of traditional cigarette as verified by exhaled carbon monoxide.</td>
</tr>
<tr>
<td>Kralikova et al., (2013).</td>
<td>Interview of people on the street</td>
<td>2012 respondents, age 34 year mean, 17 cities across the Czech republic</td>
<td>About 20% of smokers who try e-cigs go on to become regular e-cig users.</td>
</tr>
<tr>
<td>Pokhrel et al., (2013)</td>
<td>Cross sectional survey of Hawaiians recruited from 2010 to 2012</td>
<td>1567 respondents divided in two groups .ever e-cig users(n = 202) mean age 42 ± 1 years , never e-cig users (n = 1365), mean age 46 ± 0.4 years</td>
<td>Smokers who tried E-cigs is more confident to quit smoking .</td>
</tr>
</tbody>
</table>
Attitude towards Electronic Cigarettes

The review on chemical analysis, address the safety of the e-cigs. It has been found that, nicotine content of the e-liquids in the cartridges from some brands, failed to claim labelled and actual nicotine content. (Goniewicz et al., 2013; Cameron et al., 2014) and also many questions are raised for the contents of E-cigs, even though there is more comprehensive knowledge of the chemical constituents of e-cigarette than tobacco ones (Cahn and Siegel, 2010).

Cigarette smoke from burn tobacco products contains thousands of compounds, many of which have been exposed to promote carcinogenesis such as trace elements (i.e., cadmium, arsenic, chromium, nickel and lead), the tobacco specific N-nitrosamines (TSNA), the polyyclic aromatic hydrocarbons (PAH), and volatile organic compounds (VOCs) (Rodgman and Perfetti. 2009; Talhout R et al., 2011).

As mention above the main basic ingredients of E-cigs liquids are propylene glycol and glycine. Propylene glycol is considered generalized recognized as safe (GRAS) by the U.S. Food and Drug Administration (USFDA). But the literature survey revealed that it can cause eye and respiratory irritation, long and repetitive inhalation may affect central nervous system (MDSS,Scientelab.com).When propylene glycol heated or vaporized can form propylene oxide and as per international agency for research on cancer it is class 2B carcinogen (Saino et al., 2012),whereas glycine heating may forms acrolen, which can causes upper respiratory tract irritation(U.S EPA).some physical injuries and illness also reported by e-cig use, due to explosions and fires (Chen IL, 2012; CBS News 16, 2012).

Studies on Chemical Analysis of E-Cigarette

The studies shown unsuitable impact of e-cigarette and vaping on health.

Bahi et al., (2012) mention mixed response of e-cigarette on Human embryonic stem cells and human fibroblasts carried out on In vitro cultures. The study shown that, nicotine in e-cigarette refill fluid had no cytotoxic effect on the Human embryonic stem cells where as the number and concentration of chemicals other than nicotine used to flavour e-cigarette refill fluids increased cytotoxicity.

McCauly et al., (2012) mention in a case report that, stopping of e-cigarette use cleared the exogenous lipid pneumonia in a 42 year old woman, but the case study does not publicized that patient is a current or ex-smoker (McCauly et al., 2012).

A case of atrial fibrillation in an elderly person after E-cig use has been reported. But report further explains, this could be the effect of nicotine on autonomic nervous system (Monroy, A.E et al., 2012).

A study done by Vardavas et al., (2012) on 10 healthy smokers to find out the effect of E-cigs on pulmonary functions shown, after acute ad libitum puffing from e-cig (Nobacco,11 mg/ml of nicotine) for five minutes, found no effect on spirometry but shown 18% dynamic airway resistance and 16% decreased expired nitric oxide. The limitation of this study is small sample size. Even though this study suggest that e-cigs constricts peripheral airways which could be particular concern to COPD, Asthma, emphysema and bronchitis people and some authors conclude this effect, is a sign of pulmonary inflammation (Schober et al., 2013).

A case report by thota, and latham, (2014) mention, electronic cigarettes possibly associated with acute eosinophilic pneumonitis (AEP) in a previously healthy 20 year old active-duty sailor. The data suggested that, there could be a link between use of e-cig and AEP. But author further stated that studies are needed to establish a correlation between these two (Thota, and Latham, 2014).

An outline of the studies involving safety of e-cig summarized in the Table 2.
The studies involving chemical analysis of e-cigs summarized in the Table 3.

The analysis done by (Cheah et al., 2012; Cameron et al., 2013) on various brands of e-cigs cartridges and solution to determine the nicotine and its impurities reported that, Variable nicotine content in cartridges of same brands, inconsistency with product labelling and misleading information on labels raised e-cig safety (Cheah et al., 2012; Cameron et al., 2013).

Similar to above study, another investigation done by Etter et al., (2013) on numerous brands of e-cig refill solutions, revealed nicotine content to be precise and reliable to what was printed on the label (Etter et al., 2013).

Thota and latham (2014). Case report Atrial fibrillation Elderly person E-cig reported to induced atrial fibrillation.

Farsalinos et al., (2014). eGO-T battery (nobacco ,Athens , greece) 36 healthy smokers average age 36 ± 5, 40 E-cig users average age 35 ± 5 Ecocardiographic examination and myocardial performance index before and after use of tobacco cig and E-cigs E-cigs does not show any immediate effect on myocardial function whereas tobacco cig causes delay in myocardial relaxation.

Table 3. summary of studies described safety of Electronic cigarettes.

<table>
<thead>
<tr>
<th>Authors</th>
<th>E-cig brands</th>
<th>Parameters tested</th>
<th>Study Design</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eisenberg et al., 2010</td>
<td>Njoy Crown Seven</td>
<td>Plasma nicotine and heart rate measured before and after 10 puffs of each device on four different groups.</td>
<td>16 smokers, naïve to e-cigarettes were cycled through the four different groups</td>
<td>Smoking, but not vaping, raised plasma nicotine and heart rate.</td>
</tr>
<tr>
<td>Vansickle et al., 2010</td>
<td>Njoy Crown Seven</td>
<td>Plasma nicotine, carbon monoxide and heart rate taken before and after 10 puffs on different groups</td>
<td>16 smokers, naïve to e-cigarettes were cycled through the four different groups.</td>
<td>Nicotine, expired carbon monoxide heart rate all raised after smoking, a but not vaping</td>
</tr>
<tr>
<td>Etter and Bullen., 2011</td>
<td>Own brand e-cig</td>
<td>Salivary cotinine and heart rate</td>
<td>E-cig users vaped ad libitum but abstained from cigarette and NRT for 48 hrs.</td>
<td>Vaping and smoking induced similar increased in salivary cotinine and heart rate.</td>
</tr>
<tr>
<td>Czogala et al., 2012</td>
<td>Not mention</td>
<td>Systolic pressure, Diastolic pressure, Pulse, Heart rate</td>
<td>Hemodynamic parameters are measured in smokers after smoking cigarette or vaping</td>
<td>Vaping e-cigarettes fail to induce the typical hemodynamic parameters linked with traditional smoking.</td>
</tr>
<tr>
<td>Vansickle et al., 2012</td>
<td>Vapour King</td>
<td>Plasma nicotine concentration, heart rate, urge to smoke cigarette, and nicotine withdrawal symptoms tested in four smokers</td>
<td>Twenty smokers ,not currently using e-cig were cycled through four experimental sessions</td>
<td>e-cig substantially deliver nicotine, increase heart rate, reduced withdrawal symptoms and urge to smoke</td>
</tr>
<tr>
<td>Dawkins and corcoron., 2013</td>
<td>First generation e-cig (18 mg/ml)</td>
<td>Tobacco withdrawal symptoms Urge to smoke</td>
<td>14 E-cig users abstinent from smoking and vaping for 12 hr before test period.</td>
<td>Vaping helped in reducing tobacco related withdrawal symptoms and urge to smoke.</td>
</tr>
<tr>
<td>Farsalinos and Romagana., 2013</td>
<td>Case report</td>
<td>A 28 year old male with chronic idiopathic neutrophilia</td>
<td>Smoking abstinence and use of e-cig reversed symptoms of chronic idiopathic neutrophilia.</td>
<td></td>
</tr>
<tr>
<td>Flouris et al., 2013</td>
<td>Giant,Nobacco GP Greece (11mg/ml)</td>
<td>Repeated measures controlled study</td>
<td>30 smokers gone through a control session, active smoking and active vaping session</td>
<td>e-cig use induced smaller changes in pulmonary function but similar nicotinergic impact compared to smoking</td>
</tr>
<tr>
<td>Vansickel and Eissenberg., 2013</td>
<td>Own brand</td>
<td>Plasma nicotine Heart rate</td>
<td>Blood samples were collected at baseline and after 1 hr ad libitum</td>
<td>Vaping and smoking induced similar increased in plasma nicotine and heart rate</td>
</tr>
<tr>
<td>Thota and latham ,2014</td>
<td>Case report</td>
<td>Acute eosinophilic pneumonitis(AEP).</td>
<td>E-cig possibly associated with eosinophilic pneumonitis in a previously healthy active-duty sailor.</td>
<td>The data suggested that, there could be link between use of e-cig and AEP. Further studies are needed to establish a correlation.</td>
</tr>
<tr>
<td>Monroy. A.E et al., 2012</td>
<td>Case report</td>
<td>Atrial fibrillation</td>
<td>Elderly person</td>
<td>E-cig reported to induced atrial fibrillation.</td>
</tr>
</tbody>
</table>

DISCUSSION

Electronic cigarettes use or vaping gaining attractiveness worldwide. Their usage is greatly debatable as scientific outlook. Despite rapid market penetration of e-cigs still many question are unclear about their safety, efficacy for harm reduction and total impact on public health. Now e-cig becomes a global debate, with authorities wanting to ban it or legalize it. Given the debated nature to e-cigs, the medical
Table 3. Summary involved Studies of Chemical Analysis of Electronic Cigarettes.

<table>
<thead>
<tr>
<th>Authors</th>
<th>E-cig brands</th>
<th>Substance tested</th>
<th>Analysis</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laugesen (2008)</td>
<td>Ruyan</td>
<td>TSNA, MAO-A and B inhibitors, PAH, Heavy metals, CO</td>
<td>LC-MS, Fluorometric assay GS-MS, ICP-MS, CO analyser</td>
<td>TSNAs found but much lower than tobacco cigarette not carcinogenic level, PAH, heavy metals undetectable. Exhaled eCO does not increase after e-cigarette use.</td>
</tr>
<tr>
<td>Westenberger (2009)</td>
<td>Njoy, Smoking every Where</td>
<td>TSNA, DEG, Tobacco specific impurities</td>
<td>LC-MS, GC-MS, GC-MS</td>
<td>TSNA, DEG present, Tobacco specific impurities present Measured Nicotine in several e-cig solutions is irregular to be in safe.</td>
</tr>
<tr>
<td>Hadwiger et al. (2010)</td>
<td>Not mention</td>
<td>Amino Tadalafil Rimonabant</td>
<td>HPLC-DAD-MMI-MS</td>
<td>Amino tadalafil and Rimonabant present Presence of nicotine in products labelled as containing no nicotine</td>
</tr>
<tr>
<td>Trehy et al. (2011)</td>
<td>Njoy, Smoking every Where</td>
<td>Related impurities</td>
<td>HPLC-DAD</td>
<td>Nicotine related impurities present.</td>
</tr>
<tr>
<td>Cheah et al. (2012)</td>
<td>20 different brands of e-cigs</td>
<td>Nicotine contents in cartridges and e-cig quality</td>
<td>GC-MS and Visual inspection of product</td>
<td>Variable nicotine content in cartridges of same brands, inconsistency with product labelling and misleading information on labels raised e-cig safety.</td>
</tr>
<tr>
<td>Gontiewicz et al. (2012)</td>
<td>eleven polish brands and one English brands</td>
<td>Carboxyls, VOC TSNA, Heavy metals.</td>
<td>HPLC-DAD,GC-MS, UPLC-MS, ICP-MS</td>
<td>TSNA, VOC, and carbonyl compounds were found to be 9 to 450 times lower in e-cigs mist compare to conventional cigarette smoke.</td>
</tr>
<tr>
<td>McAuley et al. (2012)</td>
<td>Not mention</td>
<td>TSNA, PAH, DEG, VOC Carbonsyls</td>
<td>GC/MS, GC/MS, GC/MS, HS/MS HPLC-UV</td>
<td>TSNA, PAH, diethylene glycol, VOC, and carbonyls in e-cigarette mist were all negligible compared to cigarette smoke.</td>
</tr>
<tr>
<td>Pellegrino et al. (2012)</td>
<td>Italian brands of e-cigarettes</td>
<td>Particulate matter</td>
<td>Particle counter and smoking Machine</td>
<td>Particulate matter found in E’cig mist but lesser than cigarette smoke.</td>
</tr>
<tr>
<td>Schripp et al. (2012)</td>
<td>Three unidentified brands</td>
<td>VOC, Particulate Matter</td>
<td>GC-MS, Particle counter and smoking machine.</td>
<td>VOC in e-cig cartridges, solution and mist but lower than tobacco cigarette, PM is low in e-cig mist compared to cigarette smoke.</td>
</tr>
<tr>
<td>Cameron et al. (2013)</td>
<td>Vapour liquid Smart smoke, BE112 No brand liquid</td>
<td>Nicotine content in solutions and cartridges</td>
<td>LC-MS</td>
<td>Nicotine levels in e-cig solutions were too irregular to be reflected unsafe.</td>
</tr>
<tr>
<td>Kim and Shin (2013)</td>
<td>105 liquids brands from 11 korean e-cig companies</td>
<td>TSNA</td>
<td>LC-MS</td>
<td>TSNA are present at low levels in e-cigarette replacement fluids</td>
</tr>
<tr>
<td>Etter et al. (2013)</td>
<td>10 brands of refill liquids</td>
<td>Nicotine contents, nicotine degradation and its impurities</td>
<td>GC and LC</td>
<td>Measured Nicotine content in refill liquids are similar as indicated on the label. Impurities found but below dangerous level.</td>
</tr>
<tr>
<td>Williams et al. (2013)</td>
<td>Not mention</td>
<td>Heavy metals Silicate particles</td>
<td>ICP-MS, Particle counter and smoking machine, light and electron microscope, cytotoxicity testing, x-ray, Microanalysis</td>
<td>Heavy metals and silicate particles found in e-cig mist</td>
</tr>
</tbody>
</table>

Abbreviations: TSNA= tobacco specific nitrosoamines; PM=particulate matter; LC-MS = liquid chromatography-mass spectrometry; MAO-A and B = monoamine oxidase A and B; PAH = polycyclic aromatic hydrocarbons; GS-MS = gas chromatography - mass spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; CO = carbon monoxide; VOC = volatile organic compounds; UPLC-MS = ultra-performance liquid chromatography-mass spectrometry; HPLC-DAD-MMI-MS = high performance liquid chromatography-diode array detector-multi-mode ionization-mass spectrometry.

community are in quandary to advice this as a smoking cessation aid to their patients. Most of the studies reported mixed response regarding e-cig effectiveness and safety. Maximum of the studies done on internet, that is consumer based surveys regarding personal view on vaping, some observational studies (Caponnetto, Polosa, Russo, Leotta, & Campagnia, 2011; Farsalinos & Romagna, 2013; Schneiderhan, 2012), few randomized trials (Bullen et al., 2013; Caponnetto, Campagna, et al., 2013), one large scale cross sectional study (Brown et al., 2014) Suggest that e-cigs help smokers quit or reduce smoking. Outside these clinical studies, few longitudinal studies of vapers have been published (Adkison et al., 2013; Vickerman, Carpenter, Altman, Nash, & Zbikowski, 2013) and it is still unclear how the behaviour of vapers evolves over time. The evaluation from above limited studies on inadequate participants with short time periods from some countries on electronic cigarettes without sufficient data worldwide about its safety, effectiveness and health impact cannot accomplish e-cigarettes is harmless in complete terms. In order to conclude firmly, still more research is needed globally in different population to look at its long-term safety and effectiveness particularly on cardiovascular diseases and on smoker’s health from different parts of the world. Our literature survey shown USA,
UK, Italy, Greece, new Zealand, Switzerland have higher E-cigs research output compare to other countries of the world, this indicate us there is necessity of E-cigs research globally including Malaysia to a make generalised statement about its safety and effectiveness.

Although our literature survey from 2004 onwards but we found first article as per our objective topic in 2008. E-cigs research emerging more from 2009 to present date, indicating that research in progress. Despite its availability in most the countries except some countries they ban sale of electronic cigarettes with nicotine (Australia, Brazil, Canada, Mexico, Panama, Singapore and Switzerland) the data is lacking country wise including Malaysia.

In our review literature survey many authors concluded that many questions about E-cigs use are unanswered, primarily effectiveness of this device as a smoking cessation aid, long term users and device safety and it use might promote nicotine addiction in non-smokers especially youth generation and has potentiality to renormalize smoking act. Presently very little research has been carried on human health in some nations. Existing available few studies largely conducted on healthy peoples with short time exposure revealed that, minor side effects like mouth irritation, dry cough, nausea, vomiting and with little or no effects on pulmonary and cardiovascular functions without any serious side effects and withdrawal symptoms have been reported with e-cig use. But lot of questions upraised about the safety of its basic contents like propylene glycol that cause respiratory irritation, bronchial constriction and about engineering of the device. The study conducted by FDA found TSNAs and DEG, PAH, VOC and some trace elements in lower quantities, detected in electronic cigarettes cartridges, solutions and mist, open lot of questions regarding its quality, regulations and health issues.

Our study is not without limitations, as per the topic and searching key words and narrative nature of this manuscript only original articles that reported mainly safety, effectiveness and chemical analysis of electronic cigarettes in above mention databases were included. Despite some articles cited with other topics or key words might be missed and might give some important information regarding safety and effectiveness of E-cigs. Additionally articles published other than these data-banks and published in other languages such as German and French were not selected, might give some important information regarding safety and effectiveness was missed.

CONCLUSION

Due to limited studies with inadequate participants and short time exposure in some developed countries, e-cig cannot accomplish safe and effective. In order to conclude decisively, still more research is required globally in different population to look at its long-term safety and effectiveness particularly on cardiovascular diseases and on smoker's health from different parts of the world including Malaysia. Hence, the current literature review does not warrant a conclusion that electronic cigarettes are safe and effective smoking aid in absolute terms. In view of this, it is important to investigate and establish the long term safety and effectiveness of these devices in order to ensure that, the decisions of regulators, healthcare providers and consumers are based on science.

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Table 4. Maximum Tobacco Specific Nitrosamine (TSNAs) Levels in Different Cigaretttes and Nicotine-Delivery Products (Cahn and Siegel, 2010)

<table>
<thead>
<tr>
<th>Product</th>
<th>NNN (mcg)</th>
<th>NkK (mcg)</th>
<th>NAT (mcg)</th>
<th>NAB (mcg)</th>
<th>Total (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicorette gum (4 mg)</td>
<td>2.00</td>
<td>ND</td>
<td>ND</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>Nicoderm CQ patch (4 mg)</td>
<td>ND</td>
<td>8.00</td>
<td>ND</td>
<td>8.00</td>
<td></td>
</tr>
<tr>
<td>Electronic cigarettes</td>
<td>3.87</td>
<td>1.46</td>
<td>2.16</td>
<td>0.69</td>
<td>8.18</td>
</tr>
<tr>
<td>Swedish snus</td>
<td>980</td>
<td>180</td>
<td>790</td>
<td>60</td>
<td>2010</td>
</tr>
<tr>
<td>Winston (full)</td>
<td>2200</td>
<td>580</td>
<td>560</td>
<td>25</td>
<td>3365</td>
</tr>
<tr>
<td>Newport (full)</td>
<td>1100</td>
<td>830</td>
<td>1900</td>
<td>55</td>
<td>3885</td>
</tr>
<tr>
<td>Marlboro (ultra-light)</td>
<td>2900</td>
<td>750</td>
<td>1100</td>
<td>58</td>
<td>4808</td>
</tr>
<tr>
<td>Camel (full)</td>
<td>2500</td>
<td>900</td>
<td>1700</td>
<td>91</td>
<td>5191</td>
</tr>
<tr>
<td>Marlboro (full)</td>
<td>2900</td>
<td>960</td>
<td>2300</td>
<td>100</td>
<td>6260</td>
</tr>
<tr>
<td>Skoal (long cut straight)</td>
<td>4500</td>
<td>470</td>
<td>4100</td>
<td>220</td>
<td>9290</td>
</tr>
</tbody>
</table>

Abbreviations: NNN = 4-(methylhNitrosamino)-1-(3-pyridyl)-1-butanone; NNK = N'-nitrosonornicotine; NAT = N'-nitrosoanatabine; NAB = N'-nitrosoanabasine.

ND = Not detected.

Table 5. Levels of toxicants in E-cigs Aerosol compared with nicotine inhaler and tobacco smoke (Goniewicz et al., 2014)

<table>
<thead>
<tr>
<th>Level of toxicants</th>
<th>Content in Aerosol from 12 E-cig samples/15 puffs</th>
<th>Content in mainstream smoke from 1 cigarette</th>
<th>Content in Nicotine inhaler mist Per 15 puffs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formaldehyde, mcg</td>
<td>0.2-5.61</td>
<td>1.6-52</td>
<td>0.2</td>
</tr>
<tr>
<td>Acetaldehyde, mcg</td>
<td>0.11-1.36</td>
<td>52-140</td>
<td>0.11</td>
</tr>
<tr>
<td>Acrolein, mcg</td>
<td>0.07-4.19</td>
<td>2.4-62</td>
<td>ND</td>
</tr>
<tr>
<td>o-Methylbenzaldehyde, mcg</td>
<td>0.13-0.71</td>
<td>...</td>
<td>0.07</td>
</tr>
<tr>
<td>Toluene, mcg</td>
<td>ND-0.63</td>
<td>8.3-70</td>
<td>ND</td>
</tr>
<tr>
<td>p-m-xylene, mcg</td>
<td>ND-0.2</td>
<td>...</td>
<td>ND</td>
</tr>
<tr>
<td>NNK, ng</td>
<td>ND-0.0043</td>
<td>0.0005-0.19</td>
<td>ND</td>
</tr>
<tr>
<td>NNK, ng</td>
<td>ND-0.00283</td>
<td>0.012-0.11</td>
<td>ND</td>
</tr>
<tr>
<td>Cadmium, ng</td>
<td>ND-0.022</td>
<td>...</td>
<td>0.003</td>
</tr>
<tr>
<td>Nickel, ng</td>
<td>0.011-0.029</td>
<td>...</td>
<td>0.019</td>
</tr>
<tr>
<td>Lead, ng</td>
<td>0.003-0.457</td>
<td>...</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Safety and Effectiveness of Electronic Cigarettes


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Robertson OH, Loosli CG, Pack TT, et al. (1947). Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapour inhalation and oral administration. J Pharmacol Exper Ther, 91, 52-76.


