



EVALUATING COSTS, PERCEPTION, SATISFACTION,
SAFETY AND EFFECTIVENESS TOWARDS
ELECTRONIC CIGARETTE AT KUANTAN AND
PEKAN, PAHANG, MALAYSIA

BY

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ABSTRACT

Studies are currently lacking regarding long-term effectiveness and safety of electronic cigarette (e-cig) among single users (SUs) and dual users (DUs) whom represent the real world population of vapers community. The primary outcomes of this study were complete nicotine abstinence rate and safety issues between both groups of users at week 52. The secondary outcomes were tobacco cigarette (TCG) only abstinence and $\geq 50\%$ reduction at week 52. Users' perception, satisfaction, cost utilisation and nicotine estimation in their e-liquids were also analysed. A one year follow-up observational study was conducted among 220 regular e-cig users age >18 to 65 years from Kuantan and Pekan, Pahang, Malaysia who used e-cig for at least one month prior. The e-cig users were categorised as either SUs (used only e-cig, verified by exhaled carbon monoxide (eCO) of <8 ppm), and DUs (used both e-cig and TCG, with eCO of ≥ 8 ppm). At week 52, 15.9% of SUs (n=11) vs. 6.8% of DUs (n=10) quit both TCG and e-cig, OR: 2.57; $p = 0.048$. Whereas 34.8% of SUs (n=24) vs. 17.1% of DUs (n=25) quit only TCG, OR: 2.58; $p = 0.005$. Among the DUs 23.3% (n=34) reduced $\geq 50\%$ TCG consumptions vs. 21.7% of SUs (n=15), OR: 1.092; $p = 0.863$. Concerning safety issues, SUs perceived less e-cig adverse effects and withdrawal symptoms as compared to DUs. The major adverse effects and withdrawal symptoms observed between both groups were coughing, breathing problems and craving for TCG smoking. Moreover, seven possible smoking-related diseases such as COPD, angina, diabetes and two cases of hypertension were diagnosed among DUs, whereas in SUs a case of hypertension and diabetes each was detected. Analysis of 69 e-liquids by GC-MS showed high discrepancies between the label and actual nicotine concentration in more than 85% of the samples. Related to perception of e-cig use, 33% of both groups were satisfied and ranked it is an effective smoking cessation aid. Regarding e-cig cost utilisation, a total monthly average cost of MYR132.45, was spent which is less than that for conventional TCG use, reported as 178.80 MYR that calculated by the Global adult tobacco survey Malaysia (2011). The study concludes that e-cig can be used as an aid for complete nicotine abstinence among both the SUs and DUs. However, e-cig SUs are more likely to have total nicotine abstinence than DUs. Similarly, SUs are more likely to be TCG abstinent than DUs. However, e-cig is equally effective in SUs and DUs for TCG reduction. No serious adverse effects related to e-cig were detected. However, the safety of e-cig use in absolute term needs to be validated further. The nicotine analysis reveals an urgent need for manufacturing and quality standards of e-liquids in Malaysia. Both users generally have good perception and satisfaction towards e-cig after long-term use. However, more SUs had positive perception and satisfaction than DUs. Monthly cost expenditure of both the e-cig users is less as compared to TCG smokers.

خلاصة البحث

تفتقر الدراسات الحالية إلى تعيين مدى فعالية وسلامة السجائر الإلكترونية على المدى الطويل بين مختلف أنواع المستخدمين لتلك السجائر سواء المستخدمين لها فقط (المستخدم أحادي) أو المستخدمين لها إلى جانب سجائر التبغ التقليدية (المستخدم ثنائي). وكانت الأهداف الأولية للدراسة هي تقييم التوقف والامتناع عن كل من سجائر التبغ التقليدية و السجائر الإلكترونية وكذلك دراسة وتقييم سلامة وأمان استخدام السجائر الإلكترونية خلال فترة بين جميع المستخدمين على حد سواء في الأسبوع 52. بعد ذلك تم تصميم دراسة مدتها سنة واحدة لمتابعة عينة مكونة من 220 من المستخدمين المنتظمين للسجائر الإلكترونية لمدة شهر واحد في مدينتي كوانتان وبكان بولاية باهانج بماليزيا على الأقل تتراوح أعمارهم بين 18-65 عام وفي حالة صحية جيدة. وفيما يتعلق بالسلامة، أحادي الاستخدام كانوا أقل عرضة للآثار السلبية وأعراض الانسحاب مثال: السعال، ومشاكل في التنفس والرغبة الملحة للتدخين مقارنة بثنائي الاستخدام. علاوة على ذلك، تم رصد سبعة حالات مرضية ربما تكون ذات صلة بين كل المستخدمين بواقع حالة واحدة من حالات مرض الانسداد الرئوي المزمن، والذبحة الصدرية، ومرض السكري واثنين من حالات ارتفاع ضغط الدم بين ثنائي الاستخدام، بينما حالة واحدة من حالات ارتفاع ضغط الدم ومرض السكري بين أحادي الاستخدام وذلك خلال فترة الدراسة بأكملها. وأظهر تحليل 69% من السوائل الإلكترونية من خلال GC-MS التناقضات بين تركيز النيكوتين الفعلي والمعلن في مجمل 85% من العينات التي تم فحصها. إجمالاً كان الانطباع الجيد نحو استخدام السجائر الإلكترونية كوسيلة مساعدة للإقلاع عن التدخين بين 33% من كلا نوعي المستخدمين. وفيما يتعلق باستخدام السجائر الإلكترونية، فإن كلا نوعي المستخدمين ينفقون متوسط تكلفة شهرية يبلغ 132.45 رنجت ماليزي، وهو أقل بالمقارنة مع التبغ التقليدي، الذي ينفق عليه المدخن الماليزي 178.80 رنجت ماليزي شهرياً. ومع ذلك، فإن أحادي الاستخدام أكثر احتمالاً لامكانية الامتناع عن النيكوتين و تدخين التبغ التقليدي من ثنائي الاستخدام علي الرغم أن التقليل من تدخين التبغ كان متساو بين كلا نوعي المستخدمين للسجائر الإلكترونية. لم يتم الكشف عن أي آثار ضارة خطيرة تتعلق بالسجائر الإلكترونية. ومع ذلك، فإن استنتاج ان استخدام السجائر الإلكترونية آمن في المدى المطلق يحتاج لمزيد من البحث والدراسة. كشفت الدراسة الحاجة الملحة لمعايير الجودة والتصنيع للسوائل الإلكترونية في ماليزيا. كلا نوعي المستخدمين عموماً لديهم تصور جيد ورضاً تجاه استخدام السجائر الإلكترونية على المدى الطويل. إجمالاً كانت نفقات التكلفة الشهرية لكل مستخدم السجائر الإلكترونية أقل بالمقارنة مع المدخنين للتبغ التقليدي.

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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LIST OF ABBREVIATIONS

APV	Advance Personal Vaporizers
AIDS	Acquired Immune Deficiency Syndrome
CDC	Centre of Disease Control and Prevention
CDCR	Control of Drugs and Cosmetics Regulations
COPD	Chronic Obstructive Pulmonary Diseases
CAD	Coronary Artery Diseases
CPTR	Control for Tobacco Products Regulation
DUs	Dual Users
DSM	Diagnostic and Statistical Manual
DEG	Diethylene Glycol
E-cig	Electronic Cigarette
ENDS	Electronic Nicotine Delivery System
eCO	Exhaled Carbon Monoxide
ECG-MFTND	E-cig Modified Fagerstrom Test for Nicotine Dependence
ECG-MGNVBQ	E-cig Modified Glover Nilsson Vaping Behavioural Questionnaire
AEP	Eosinophilic Pneumonitis
FTND	Fagerstrom Test for Nicotine Dependence
FEV ₁	Forced Expiratory Volume in one Second
FEF ₂₅	Forced Expiratory Flow by 25 %
FRA _s	Formaldehyde Releasing Agents
FCTC	Framework Convention on Tobacco Control
GNSBQ	Glover Nilsson smoking Behavioural Questionnaire
GABA	Gama Aminobutyric Acid
GRAS	Generally Recognized As Safe
GC-MS	Gas Chromatography-Mass Spectrometry
HPLC	High Performance Liquid Chromatography
HPLC-DAD	High-Performance Liquid Chromatography-Diode Array Detector
ITT	Intention to Treat Analysis
IRAC	International Agency for Research on Cancer
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IS	Internal Standard
ITC	International Tobacco Control
IIUM	International Islamic University of Malaysia
LED	Light Emitting Diode
LC-MS	Liquid Chromatography-Mass Spectrometry
MAO-A and B	Monoamine Oxidase A and B
MYR	Malaysian Ringgit
MEVTA	Malaysian E-vaporizers and Tobacco Alternative Association
GATS	Malaysian Global Adult Tobacco Survey
MSD	Mass Selective Detector

NIDA	National Institute of Drug Abuse
nAchRs	Nicotinic Acetylcholine Receptors
NAc	Nucleus Accumbens
NRT	Nicotine Replacement Therapy
NECS	National E-Cigarette Survey
NHMS	National Health and Morbidity Survey
NET	Natural Extract of Tobacco
NMR	Nuclear Magnetic Resonance
NMRR	National Medical Research Registration
NCSCCT	National Centre for Smoking Cessation and Training
PM	Particulate Matter
ppm	Parts Per Million
%COHb	Percentage Carboxyhemoglobin
PFC	Prefrontal cortex
PHE	Public Health England
PAH	Polycyclic Aromatic Hydrocarbons
%DF	Percentage Difference
PG	Propylene Glycol
RCP	Royal College of Physicians
RCTs	Randomized Clinical Trials
IREC	IIUM Research Ethics Committee
MNWS-R	Revised Minnesota Nicotine Withdrawal Scale
SUs	Single Users
SPMA	S-phenylmercapturic acid
SPSS	Statistical Package for the Social Sciences
SD	Standard Deviation
TCG	Tobacco Cigarette
TQD	Targeted Quit Date
THR	Tobacco Harm Reduction
TSNA	Tobacco Specific N-nitrosamines
UPLC-MS	Ultra-Performance Liquid Chromatography-Mass Spectrometry
USDHHS	United State Department of Health and Human Services
USFDA	United State Food and Drug Administration
USEPA	United State Environmental Protection Agency
VTA	Ventral Tegmental Area
VV	Variable Voltage
VW	Variable Wattage
VOC	Volatile Organic Compounds
VG	Vegetable Glycerine
WHO	World Health Organization
3-HPMA	3-Hydroxypropyl Mercapturic Acid
2-HPMA	2-Hydroxypropylmercapturic acid
1-HOP	1-Hydroxypyrene
HMPMA	3-Hydroxy-1-Methylpropyl Mercapturic Acid

CHAPTER ONE

INTRODUCTION

1.1 CIGARETTE SMOKING

Tobacco smoking damages practically every organ of human body and it is one of the leading causes of several health complications in various countries in the world. Tobacco use induces numerous illnesses and the decline in physical condition of a smoker in general (World Health Organisation [WHO], 2015). Smoking is a major reason of loss of human lives and ill health in developing nations. Tobacco cigarette (TCG) usage is rising worldwide and it is one of the chief threats to existing and future global health (WHO, 2015). TCG abstinence is one of the ultimate economic strategies, which medical doctors and other health authorities could organise to increase the lifespan of their patients. There is a considerable relation between high TCG use and its duration with smoking illnesses. Moreover, studies revealed that heavy tobacco use is associated with a greater threat with mortality (Wilson, Gibson, Willan and Cook, 2000). Abstinence of TCG use at any phase of smoking owing to a significant reduction in risks associated with smoking (Benowitz, 2008).

According to the U.S. National Institute of Drug Abuse (NIDA, July 2012), cigarette is a very efficient and highly engineered drug delivery system containing more than 4,000 chemicals one of them is nicotine. Due to the pharmacological action of nicotine, smokers are dependent on TCG use (Giovino, Field, Tomar, Escobedo and Slade, 1994). Nicotine is a substance that creates both physical and psychological addictive effects to smoking. At first, some smokers believe that tobacco smoking is merely a habit, but repetitive failure to quit tobacco use made them realise that it is more of an addiction than habit, and increases their dependency to nicotine.

As per the WHO definition, drug dependence has defined as “a behavioural intention in which the usage of psychoactive medication is recognised to have severe importance over other actions which once had a considerably higher value” (Edwards, Arif, and Hodgson, 1982). In other words, the medication has resulting to regulate behaviour to a level that reflected as unsafe to the individual or whole community. Previous studies indicated that tobacco smoking is psychoactive addiction. Moreover, an average smoker requires four or more smoking cessation efforts before succeeding the complete walk out (Giovino et al., 1994). Nearly more than 95% unaided quit attempts fail to achieve the long-term smoking abstinence (Hughes, Keely, and Naud, 2004).

1.2 CHARACTERISTIC OF NICOTINE ADDICTION

Diverse criteria and definitions have described by different health organisations and authorities for drug dependence or addiction. For health concerns of smoking to nicotine addiction, US Department of Health and Human Services (USDHHS) developed the norms for medication addiction (US Surgeon General report, 2014). Nicotine met all the surgeon general reports major norms for medication dependencies, which commented that substance, must stimulate obsessive use, retain psychoactive actions, and strengthen its specific use. However, a number of additional criteria mention in the report revealed by many smokers but generally not present in all the TCG consumers. For example, certain individuals who quit smoking do not relapse and some smokers revealed that the absence of nicotine withdrawal signs when they quit smoking (US Surgeon General report, 2014; Table1.1).

Table 1.1 US Surgeon General Criteria For Drug Dependence

<ul style="list-style-type: none"> ➤ 1.Principal Norms <ul style="list-style-type: none"> • Extremely organized or obsessive use • Psychoactive action • Medication force behaviour ➤ 2.Supplementary conditions <ul style="list-style-type: none"> 2.1:Dependent manners frequently include <ul style="list-style-type: none"> • Stereotypic medication use • Usage even damaging adverse effects • Reverse to use after cessation • Repeated Medication desires 	<ul style="list-style-type: none"> 2.2: Addiction to medication frequently induce <ul style="list-style-type: none"> • Tolerance • Physical addiction • Enjoyable action(euphoric effect)
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Source: US Surgeon General Report, 2014

The American Psychiatric Association (APA) has developed other standards for drug addiction in Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-V) in tobacco use disorder segment (DSM-V, 2013, Table1.2). However, the most commonly used scale worldwide for evaluating the level of nicotine addiction is Fagerstrom Test for Nicotine Dependence (FTND). This scale created on the answer to six queries, which indicated that higher the scale score the more addicted to nicotine the subject is (Heatherton, Kozlowski, Frecker and Fagerstrom, 1991).

Table 1.2 Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
(DSM-V, 2013) Tobacco Use Disorder

<p>The pattern of medication use leads to clinical notable damage or suffering, as demonstrated by underneath standards happening at any time within a one-year period.</p> <ol style="list-style-type: none">1. Tolerance, as explained whichever of the below condition.<ul style="list-style-type: none">• The Clear necessity for greater than before dosing of the ingredient to attained the preferred action.• Significantly reduce effect with the sustained usage of a similar quantity of the ingredient.2. Withdrawal signs as established by any of the beneath conditions:<ul style="list-style-type: none">• The distinguishing elimination patterned off the ingredient.• A similar ingredient used to release or escape withdrawal signs.3. The ingredient frequently consumed in high quantity over extended time.4. Determined craving or ineffective attempt to reduce or normalize ingredient usage.5. Excessive time is consumed in actions needed to get the ingredient, for using the ingredient, or reverse to its action.6. Significant community, professional, or entertaining accomplishments are lost or diminished due to ingredient usage.7. The practice of ingredient is uninterrupted even with information that its use had an obstinate or repeated bodily or emotional problem that is possible to lead, triggered, or worsened by the ingredient.

Source: Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition
(DSM-V, 2013).

1.3 NEUROBIOLOGY OF NICOTINE ADDICTION

1.3.1 Nicotinic Acetylcholine Receptors (nAChRs)

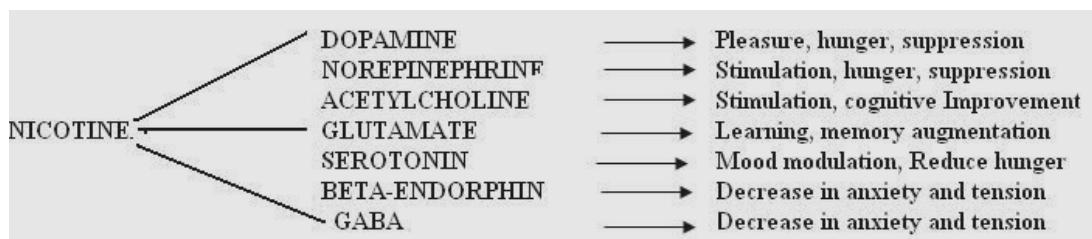
When a smoker draws a puff from TCG, nicotine quickly administered to the pulmonary venous circulation. Then it reaches the arterial circulation and transfers swiftly to the brain. In the brain, it attached to nAChRs, which is a ligand-gated ion channels. Bonding of nicotine to nAChRs releases the sodium (Na^+) and calcium (Ca^{++}) ions from the neuron cell membrane. These exchanges of cations across cell membrane activate the neurone cell, which leads to generating various neurotransmitters that produce rewarding effects of nicotine (Benowitz, 2008).

The nAChRs is a complex structure; consisting of 5 subunits which exist in both peripheral and central nervous systems. In the human brain, nearly nine α -subunits (α_2 - α_{10}) and three β -subunits (β_2 - β_4) of nAChRs are present. The plentiful subordinate receptors in human brains are $\alpha_4\beta_2$, $\alpha_3\beta_2$, and α_7 . The $\alpha_4\beta_2$ sub-classify receptor chiefly exist in the humanoid brain and it is supposed to be involved in the nicotine dependence effect.

1.3.2 Biology of Nicotine Reinforcement

Nicotine stimulates pleasing actions by associating with nAChRs on neurons in the brain, mesolimbic reward system. This leads to a release of various neurotransmitters including dopamine mainly in the Ventral Tegmental Area (VTA) and Nucleus Accumbens (NAc). This passage appears to be associated with drug-induced rewarding effects besides other regions such as the hippocampus, amygdala, and Prefrontal Cortex (PFC). Other neurotransmitters released along with the dopamine are norepinephrine, acetylcholine, serotonin, Gamma-Aminobutyric Acid (GABA), glutamate, and endorphins that mediate several actions of nicotine (figure 1.1).

Figure 1.1 Activation of Nicotine Receptor Releases Various Neurotransmitters



Source: Concept Adopted From Nicotine Addiction (Benowitz, 2008)

Nicotine also regulates dopamine discharge incoherently by interacting with nAChRs situated on the excitatory glutamatergic and inhibitory GABA neurons in the VTA. These glutamatergic and GABAergic neurons initiate a number of other brain areas such as NAc, hippocampus, amygdala, and PFC. Together glutamate and GABA neurotransmission shows vital characters in the expansion of nicotine dependence. Apart from straight and ancillary activation of various neurotransmitters liberation, prolonged TCG use diminished the brain monoamine oxidases A and B effect that alleged to increase dopamine and norepinephrine neurotransmitters level at the synapses region. Thus, enhances the action of nicotine and leads its further addiction (Markou, 2008).

1.3.3 Psychoactive Effects of Nicotine and Its Withdrawal Symptoms

In human beings, nicotine via TCG stimulates dopamine release that induces pleasure, decreases stress and anxiety. Smokers use TCG to uphold their period of alertness and to control their temper in everyday life. When an individual halts TCG withdrawal signs of nicotine emerge such as difficulty in concentration, increased appetite, craving for tobacco, insomnia, irritability, depressed mood, restlessness, anxiety (DSM-V, 2013). Hedonic dysregulation i.e. a perception that there is small pleasure in life and accomplishments no longer enjoyable also associated with smokers those who quit TCG as a withdrawal sign. The nicotine withdrawal signs in untreated smokers create mental disturbances similar in strength that realised in psychiatric patients (Hughes, 2006).

It believed that comparative shortage in dopamine discharge together with prolonged nicotine interaction is responsible for various behavioural disorders, tobacco craving and anhedonia (perception of displeasure). Thus, pharmacological

action of nicotine dependence may assume as a mixture of both positive and negative effects in human beings. The supply of nicotine generates positive effects in smokers such as mood and functioning enhancement. However, in the absence of nicotine, smokers have recognised its negative consequences such withdrawal symptoms.

1.4 MALAYSIA AND GLOBAL TOBACCO USE:

Currently, around 1.3 billion individuals involved in tobacco smoking and it anticipated to reaching 1.6 billion by 2025. Smoking produces extensive challenges to the country's health care system and monetary burden to undeveloped nations. According to the WHO, tobacco use is the third leading cause of all death worldwide. At present, smoking is responsible for 7 million deaths globally (WHO, 2017) and it is anticipated to touch 8.3 million by 2030 (Mathers and Loncar, 2006).

In Malaysia, 20000 deaths have reported annually due to smoking-related diseases (Fathelrahman et al., 2009; National Health and Morbidity survey [NHMS], 2015). However, as per Malaysian clinical management guidelines on TCG addiction (Mahayiddin, Mazlan, and Bakar, 2003), it will reach 30000 by the year 2030. The Malaysian Global Adult Tobacco Survey (GATS, 2011) reported 43.9% of men, 1.0% of women, and 23.1% over-all (4.7 million adults) were current tobacco smokers. The survey also reported that the majority of current smokers (56.4%) plan to quit one day, but only 6.3% smokers were planning to quit within the next month and 8.0% within the next 12 months. Among the survey, of the participants who attempted to stop TCG use in the previous 12 months, 80.3% who tried were deprived of any support, whereas merely 9.0% used pharmacotherapy such as Nicotine Replacement Therapy (NRT) and other medications.

However, as per latest NHMS (2015) the prevalence of current smokers was 22.8% and it has slightly dropped from 23.1% that was reported by GATS in 2011. The prevalence of male smokers too dropped from 43.9% in 2011 to 43.0% in 2015, but the smoking prevalence among females had greater than before from 1.0% in 2011 to 1.4% in 2015. According to NHMS (2015), nearly five million Malaysians aged 15 years and above smoked. The NHMS used the term current smokers as per Centres for Disease Control and Prevention (CDC) model that are mention in the table 1.3.

Table 1.3 Smokers Definitions as per the Centres For Disease Control And Prevention

Type of smoker	Definition
Current smoker	Smoked \geq 100 TCG in lifespan and using TCG every day or some days in last 30 days of investigation
Ever smoker	Smoked \geq 100 TCG in lifespan
Ex-smoker	Smoked \geq 100 TCG in lifetime, however, did not smoke any TCG in the last 30 days earlier investigation
Light smoker	Current smoker who smoked \leq 10 TCG per day
Moderate smoker	Current smoker who smoked between 10-20 TCG per day
Heavy smoker	Current smoker who smoked $>$ 20 TCG per day
Passive smoker	Non-smoker who expose to someone else smoke at least fifteen minutes for 3 days, in the last 7days
Initiation smoke age	Age at which TCG was first tried

Source: The Third National Health and Morbidity Survey (NHMSIII, 2006)

Heavy nicotine dependent smokers require evidence-based pharmacological and behavioural interventions. In Malaysia NRT, products and varenicline are currently approved pharmacologic agents for smoking cessation. Nicotine supplied in NRT products (e.g., gum, patch, lozenge or inhalator) support to reduce withdrawal symptoms during smoking cessation attempts. However, current approved United States Food and Drug Administration (USFDA) smoking cessation medications such as NRT, bupropion, varenicline (Table1.4) have shown good results in experimental