HEALTH TECHNOLOGY ASSESSMENT REPORT

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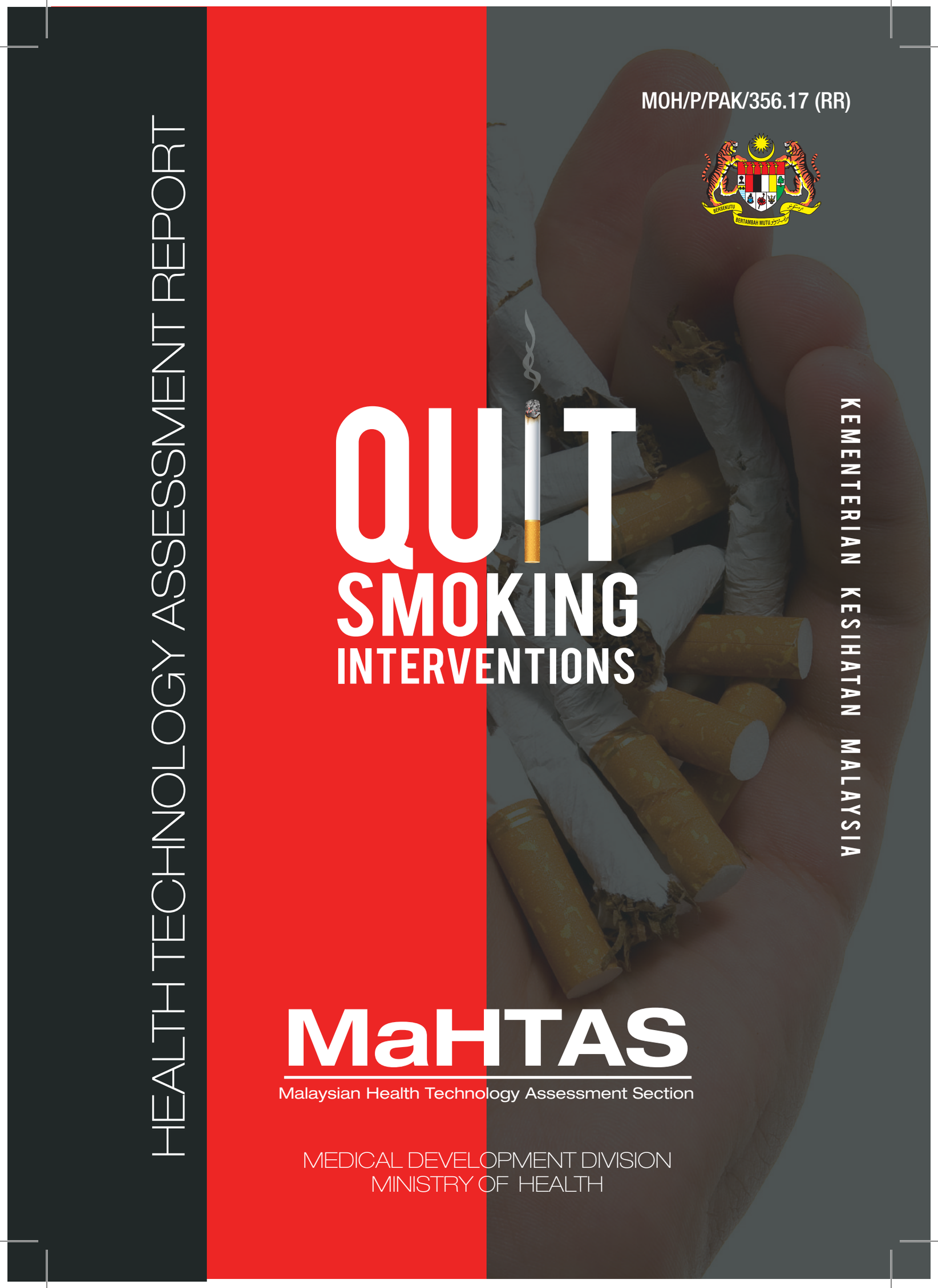

QUIT SMOKING INTERVENTIONS

KEMENTERIAN KESIHATAN MALAYSIA

MaHTAS

Malaysian Health Technology Assessment Section

MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH

DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

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EXECUTIVE SUMMARY

Background

Smoking-related diseases such as cancer and cardiovascular disease are the main causes of premature death globally and in Malaysia particularly. Global estimates of about six million people worldwide die each year from causes attributed to smoking. In Malaysia, it is estimated that one-fifth of disability adjusted life years (DALYs) and one-third of years of life lost (YLL) for Malaysians were due to smoking-related diseases. Diseases related to smoking remain the top causes of death in Ministry of Health (MOH) hospitals, accounting for more than 15% of hospitalisations and 35% of in-hospital deaths.

In Malaysia, there are 486 quit-smoking clinics and 47 hospitals within the Ministry of Health facilities throughout the country that provide smoking cessation services including promotion, screening, counselling and pharmacotherapy services. On average, around 15% to 17% of those who registered in these quit-smoking clinics eventually ceased smoking. In 2005, National Poison Centre, Universiti Sains Malaysia (USM) launched a quitline service which is carried out by the pharmacists through the telephone, supported by an online system called "Smokefree-Online System" (SOS). This system was developed to assist the providers in evaluating the status of the smokers as well as in providing advice to them through step by step procedures.

The WHO MPOWER strategy focuses on six key activities which include *monitoring* tobacco use and prevention policies, *protecting* people from tobacco smoke, *offering* help to quit tobacco use, to *warn* about the dangers of tobacco, *enforcing* bans on tobacco advertising, promotion and sponsorship and *raising* taxes on tobacco. In line with this strategy, the existing smoking cessation services in Malaysia needs to be strengthened and expanded to involve the private hospitals, clinics and the community pharmacies. Activities of screening on smoking in schools are to be strengthened through the school dental team and counseling to stop smoking by the school counselors. To date, many tobacco control measures have been undertaken in concert with the anti-tobacco media approach to promote awareness among the public about the harmful effect of tobacco through the national anti-smoking media campaign known as the "*Tak Nak Merokok*" or Say No Campaign. Therefore, a Health Technology Assessment (HTA) was requested by the Head of Tobacco Control Unit, Disease Control Division, Ministry of Health Malaysia to assess the effectiveness, safety and cost-effectiveness of various smoking cessation interventions in public and private sectors to increase quit smoking rate.

Technical features

There are two types of clinical intervention depending on the intensity of intervention and level of service provided; brief clinical intervention and intensive clinical intervention. The five major steps (5 A's) of brief intervention involves ***asking*** patients about their current smoking, ***advising*** them to stop, ***assessing*** their willingness to begin treatment to quit, offering ***assistance*** either by providing further advice, a referral to a specialist service or recommendation of or a prescription for pharmacotherapy or ***arranging*** a follow up wherever it is appropriate. The intensive clinical interventions could be provided by any suitably trained doctors and other health care providers

who have the resources available to give intensive interventions and are appropriate for any tobacco user willing to participate in them. This could be achieved by increasing the length of individual treatment sessions, the number of treatment sessions and specialised behavioural therapies. The components of an intensive tobacco dependence intervention include the assessments of willingness to make a quit attempt, programme clinician, programme intensity, programme format, type of counselling and behavioural therapies and medication used.

Pharmacotherapy of smoking cessation include either nicotine based (nicotine replacement therapy) or non-nicotine based therapy. The former includes nicotine gum, nicotine patch, nicotine inhaler, nicotine lozenges while the latter include varenicline, sustained release (SR) bupropion, and nortriptyline. Non-pharmacological therapies for smoking cessation include behavioural, psychological as well as quitlines and technological - based methods.

Policy question

Which quit smoking intervention can be used in Malaysia to increase its quit smoking rate?

Objectives

1. To assess the effectiveness of quit smoking interventions in increasing quit smoking rate
2. To assess the safety of quit smoking interventions
3. To assess the economic implications of quit smoking interventions in increasing quit smoking rate
4. To assess the ethical, legal and organizational issues related to quit smoking interventions

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R), EBM Reviews-Cochrane Database of Systematic Reviews (up to 1st Quarter 2015), EBM Reviews-Cochrane Central Register of Controlled Trials (2005 to September 2016), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2015), EBM Reviews-Health Technology Assessment (3rd Quarter 2016), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2015). Parallel searches were run in PubMed and Embase. Limits were applied to the articles published from year 2000 onwards and to study designs using meta-analysis, systematic review, clinical trials, observational studies only. The last search was run on 7 October 2016. Additional articles were identified from reviewing the references of retrieved articles. Studies were selected based on inclusion and exclusion criteria. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) tool and The Cochrane Collaboration's tool for assessing risk of bias. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force.

Results

A total of 14,571 titles were identified with seventeen were identified from references of retrieved articles. After removal of 6,582 duplicates, 8,006 titles were screened and 7172 were excluded. A total of 834 potentially relevant

abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the full text articles, 128 full text articles were included and 706 full text articles were excluded.

Effectiveness

Community based smoking cessation programme:

- Multicomponent interventions in primary care were effective, safe and able to achieve greater long-term continuous smoking cessation compared to usual care and counselling alone. Its pooled odds ratio (OR) for smoking cessation was 2.2 [95% confidence interval (95% CI) 1.7, 2.8] while for provider performance in 5As delivery i.e. for “ask”, “advice”, “assess”, “assist” (quit date),“assist”(prescribe medications) and “arrange” follow-up, the ORs were 1.79 (95% CI 1.6,2.1),1.6 (95% CI 1.4,1.8), 9.3 (95% CI 6.8,12.8), 3.5 (95% CI 2.8,4.2) and 8.5 (95% CI 5.1, 14.2), respectively
- Patients who received specialist one-to-one behavioural support were twice more likely to remain abstinent than patients seen by a general practitioner (GP) and pharmacy providers [OR 2.3 (95% CI 1.2,4.6]
- Group-based behavioural support were three times more effective compared to seen by a GP or pharmacy providers (OR 3.4; 95% CI 1.7,6.7) in achieving abstinence
- Interventions targeting smoking parents of infants or young children successfully increased the parental quit rate (23.1% in the intervention group versus 18.4% in the control group)
- Behavioural interventions by oral health professionals incorporating an oral examination component in the dental office and community setting may increase tobacco abstinence rates among smokeless tobacco users (OR 1.44, 95% CI 1.16, 1.78), although limited evidence on similar interventions for cigarette smokers
- Proactive, population-based tobacco cessation care using proactive outreach to connect smokers to telephone or in-person smoking cessation services was effective
- Increase in funding for smoking cessation services encouraged providers to promote more cessation consultations and encouraged smokers to make more cessation visits
- City-wide tobacco control policies are effective among high-risk urban communities, but linguistically and culturally-specific community-level tobacco control intervention may further increase the reduction in smoking prevalence rates
- Large scale distribution of free nicotine replacement therapy (NRT) resulted in successful quit rate among NRT recipients compared to non-recipients (33% versus 6%,p<0.0001)

Effectiveness by different types of providers:

- Physicians, nurses and psychologists were effective at helping smokers to quit. Interventions with NRT increased the effectiveness of nurses, psychologists, and providers of unknown types by almost two-folds
- Pharmacist-led interventions by community pharmacists significantly impact abstinence rates in smoking cessation interventions compared to controls [Relative Risk (RR) 2.17, 95% CI 1.43,3.31]. The use of NRT, alongside counselling, resulted in higher abstinence rates (RR 3.46, 95% CI 1.66,7.23 versus RR 1.98, 95% CI 1.24,3.16)

Hospital based smoking cessation programme:

- Intensive counselling interventions that began during the hospital stay and continued with supportive contacts for at least one month after discharge increased smoking cessation rates after discharge (RR 1.37,95% CI 1.27,1.48). Adding NRT to intensive counselling significantly increases cessation rates over counselling alone, but there was insufficient evidence on adding bupropion or varenicline
- Emergency department–initiated tobacco control combining motivational interviewing and booster phone calls showed a trend toward increased episodically measured tobacco abstinence up to 12 months.

Pharmacotherapy:

- Nicotine replacement therapy (NRT), bupropion SR, and varenicline improve the smoking cessation rates
- Nicotine replacement therapy increase smoking abstinence at six months by 53%–68%
  - Statistically significant superiority of NRT compared with placebo (RR 2.06, 95% CI 1.34,3.15)
  - Four types of NRT performed similarly against each other
  - Use of a combination of NRT products increases cessation rates more than the use of a single NRT product.
  - Comparing 8 weeks (standard), 24 weeks (extended), and 52 weeks (maintenance) of nicotine patch treatment found no difference in efficacy beyond 24 weeks of treatment in a broad group of smokers
- Bupropion SR increase smoking abstinence at six months by 49%–76%
  - Bupropion higher abstinence rates than those on placebo (OR 2.07, 95% CI 1.75,2.45)
- Head-to-head comparisons between bupropion and NRT showed equal efficacy (OR 0.99, 95% CrI 0.86,1.13)
- Varenicline was more effective than placebo in smoking abstinence OR 3.61 (95% CI 3.07,4.24)
  - Varenicline was more effective than bupropion in smoking abstinence; OR 1.75 (95% CI 1.52, 2.01)
  - Varenicline was more effective than nicotine patch (OR 1.51, 95% CrI 1.22,1.87), than nicotine gum (OR 1.72, 95% CrI 1.38,2.13), and than 'other' NRT (inhaler, spray, tablets, lozenges; OR 1.42, 95% CrI 1.12,1.79), but was not more effective than combination NRT (OR 1.06, 95% CrI 0.75,1.48)
- Combination therapy of varenicline plus NRT was more effective than varenicline alone, especially if pre-cessation treatment of nicotine patch is administrated. Adverse events of combination therapy are similar to mono-therapy except for skin reaction
- Nortriptyline increased the chances of quitting (RR 2.03, 95% CI 1.48, 2.78). Neither nortriptyline nor bupropion were shown to enhance the effect of NRT compared with NRT alone
- No evidence of a therapeutic effect of naltrexone (opiod antagonists) alone or as an adjunct to NRT on short-term or long-term smoking abstinence rates
- Clonidine increased the chances of quitting (RR 1.63, 95% CI 1.22,2.18), but this was offset by a dose-dependent rise in adverse events
- Mecamylamine in combination with NRT may increase the chances of quitting, but current evidence is inconclusive

- Cytisine increased the chances of quitting, although absolute quit rates were modest and limited evidence against NRT with no direct comparison with varenicline and other modalities
- Nicotine vaccine, NicVAX® has no difference in abstinence rates compared to placebo from weeks 9 to 52 [27.7% versus 30.0%, OR 0.89, 95% CI 0.62,1.29] or weeks 37 to 52 (33.8% versus 33.2%, OR 1.03, 95% CI 0.73,1.46).
  - No improvement in smoking cessation rates when given in addition to varenicline and behavioural support
  - Currently, NicVAX® is not yet licensed for use as an aid to smoking cessation or relapse prevention

Behavioural and psychological interventions:

- Health provider advice and counselling, group counselling, tailored self-help materials, and telephone counselling showed modest but significant increased smoking cessation at six months relative to control participants (18%–96%)
- Smokers who were offered cessation advice by a physician 76% more likely to have quit at six months or more than those who received no advice or usual care (RR 1.76, 95% CI 1.58,1.96)
- Providing more intense adjunctive behavioural support to smokers receiving pharmacotherapy may increase cessation by 9%–24%
- Combined pharmacotherapy and behavioural interventions increase cessation rates by 70%–100% compared with no or minimal treatment.

Pregnant women:

- Among pregnant women, behavioural interventions have benefit in smoking cessation and perinatal health
- Effects of NRT on smoking cessation were not significant with no evidence on its impacts on birth outcomes

Young people

Multicomponent approaches especially those incorporating elements sensitive to stage of change (Transtheoretical Theory) and using motivational enhancement and cognitive behavioural therapy have positive effect on smoking cessation

Elderly

Significant treatment effects for pharmacological (RR 3.18, 95% CI 1.89,5.36), non-pharmacological (RR 1.80, 95% CI 1.67,1.94), and multimodal interventions (RR 1.61,95% CI 1.4,1.84) compared with control group.

Mental health:

- Efficacy of the medications (varenicline, NRT, bupropion) similar for smokers with or without psychiatric disorders with varenicline superior efficacy to bupropion and nicotine patch, bupropion similar efficacy to nicotine patch
- In those with current and past depression, significant positive effect for adding psychosocial mood management to a standard smoking cessation intervention when compared with standard smoking cessation intervention alone; RR=1.47 (95% CI 1.13,1.92) and RR= 1.41 (95% CI 1.13,1.77), respectively

- Positive effect, although not significant, for adding bupropion compared with placebo in smokers with current depression (RR 1.37, 95% CI 0.83,2.27)

- Pooled results suggest that use of bupropion may increase long-term cessation in smokers with past depression
- Insufficient evidence to evaluate the effectiveness of the other antidepressants, NRT and psychosocial interventions

Other disease conditions:

- Patients with cardiovascular disease (CVD): Both behavioural therapy and pharmacotherapy are more efficacious than usual care for smoking cessation but no head to head comparison
- Diabetic patients: Pooled results did not provide evidence of efficacy for smoking cessation interventions in people with diabetes
- Oncology patients: Tobacco cessation interventions did not significantly affect cessation rates in both the short-term and long-term follow-up groups
- Chronic obstructive pulmonary disease (COPD) patients: Smoking cessation counselling combined with NRT was more effective than other combinations and single smoking cessation treatments in COPD
- Pre-operative patients (orthopaedic and general surgery): Pre-operative smoking interventions providing behavioural support and offering NRT increase short-term smoking cessation and may reduce post-operative morbidity

Other interventions:

- There is beneficial impact of mobile phone-based smoking cessation interventions on cessation outcomes. Smoking quit rates for the text messaging intervention group were 35% higher compared to the control group quit rates. Limited evidence however was found in WhatsApp and Facebook online social groups and their effectiveness for smoking relapse prevention for recent quitters
- A Malaysian study found smoking cessation intervention consisting of phone calls and counselling delivered during the first month of quit attempt to have significant higher abstinence rates compared to a standard care approach.
- Offering free NRT through a state quitline was an effective means of increasing quitline utilization and improving quit rate
- Complementary and alternative therapies
  - Acupuncture and hypnotherapy may help smokers quit but OR with wide CI; acupuncture (OR 3.53, 95% CI 1.03,12.07), hypnotherapy (OR 4.55, 95% CI 0.98, 21.01) and aversive smoking (OR 4.26, 95% CI 1.26,14.38)
  - Inadequate evidence to show whether hypnotherapy could be as effective as counselling treatment
  - There was no consistent, bias-free evidence that acupuncture, acupressure, or laser therapy compared to no intervention, sham treatment, or other interventions have a sustained benefit
  - Electrostimulation was not effective for smoking cessation
  - Yoga and meditation-based therapies may assist smoking cessation but limited number of studies available and associated methodological problems
- Competitions or incentives do not improve long-term smoking cessation, whether offered in the community, in healthcare settings or in the workplace. Rewarding participation in contests and cessation programmes may have more potential to deliver higher absolute numbers of quitters

Smokeless tobacco users:

- Varenicline, nicotine lozenges and behavioural interventions may help smokeless tobacco users to quit
- Treatment with bupropion did not result in any significant beneficial effect
- Combining nicotine lozenges and phone counselling significantly increased tobacco abstinence rates compared with either intervention alone
- High tobacco abstinence rates for self-help cessation interventions

Safety

- Most frequent adverse events by treatment group were nausea (varenicline, 25%), insomnia (bupropion, 12%), abnormal dreams (nicotine patch, 12%), and headache (placebo, 10%)
- Nicotine replacement therapy, bupropion SR, and varenicline were not associated with an increased risk for major cardiovascular adverse events
- NRT was associated with a higher rate of any cardiovascular adverse events largely driven by low-risk events, typically tachycardia
- No significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo
- Safety of other behavioural or complementary and alternative therapies have not been thoroughly documented although minor adverse events related to ear acupuncture, ear acupressure, and other auriculotherapy have been reported

Economic evaluation

- In France, providing medical support to smokers is very cost-effective with potential cost saving for lung cancer, COPD and CVD ranges from €15 million to €215 million at the five-year horizon for an initial cessation treatment cost of €125 million to €421 million
- The “Tips from Former Smokers® (Tips®) campaign resulted in a 12% relative increase in U.S population-level quit attempts. The campaign was not only successful at reducing smoking-attributable morbidity and mortality but also was a highly cost-effective mass media intervention
- “No Smoking Day” (NSD), an annual UK-wide campaign resulted in quit attempts rates of 2.8% points higher in the months following NSD compared with the adjacent months (95% CI 0.99%,4.62%)
- “Cut down to quit” (CDTQ) with NRT in smoking cessation was not cost-effective compared with abrupt quitting but highly cost-effective compared with no quit attempt
- Nationwide Korean government-supported public health centre-based smoking cessation clinics were found to be highly cost-effective at a level of 0.46% of the per capita gross domestic product
- Reimbursing smoking cessation support in the Netherlands was found to be cost-effective from a health care perspective
- In Canada, study comparing the standard course (12 weeks) varenicline, extended course varenicline (12 + 12 weeks), bupropion, NRT and unaided intervention found that both standard and extended courses varenicline to be more cost-effective than all other alternative smoking cessation interventions with the extended course being highly cost-effective compared with the standard varenicline treatment course
- A CEA of clinical smoking cessation interventions (counselling in hospital, quitline and counselling plus nicotine gum, nicotine patch, bupropion, nortriptyline or varenicline) in Thailand found counselling with varenicline and counselling with

nortriptyline to be cost-effective from societal perspective. Hospital counselling only, nicotine patch and bupropion were dominated by quitline, nortriptyline and varenicline, respectively.

- Ottawa Model for Smoking Cessation (OMSC), an intervention that includes in-hospital counselling, pharmacotherapy and post-hospital follow-up, compared to usual care among smokers hospitalised with acute myocardial infarction, unstable angina, heart failure, and COPD appears to be cost-effective from the hospital payer perspective
- Cost-effectiveness study of internet and telephone treatment for smoking cessation of the iQUITT Study found that adherence to combined internet and telephone interventions yields the highest number of quitters at the lowest cost
- Study on telemedicine counseling that was integrated into smokers' primary care clinics (Integrated Telemedicine, ITM) versus telephone counseling, found no superiority of ITM over telephone counseling for helping rural patients quit smoking
- Online advertising may be a highly cost-effective channel for low-budget tobacco control media campaigns compared to radio and print advertisements
- Among elderly (aged 50 years and above) participants who completed a 12-week smoking cessation program, extended NRT was not cost-effective but adding extended cognitive behaviour therapy was cost-effective
- Compared with usual care in COPD patients, intensive counselling and pharmacotherapy resulted in low costs per QALY gained with ratios comparable to results for smoking cessation in the general population. Compared with intensive counselling, pharmacotherapy was cost saving and dominated the other intervention
- The average WTP for an effective cessation method was USD191. Among men, the WTP was USD152 lower than among women

Organizational issues

- Improving adherence to smoking cessation medication through providing information and facilitating problem-solving can improve abstinence although limited evidence on this
- Good potential for social networking such as Facebook as an accessible, low-cost platform for engaging young adults
- Good feasibility and acceptability of a smoking cessation counselling tool among GP in comparison with the International Primary Care Respiratory Group (IPCRG) 'quit smoking assistance' tool
- Mobile phone text messaging-based smoking cessation intervention appears feasible and acceptable
- Good feasibility of connecting patients in primary care settings to state-level quit lines
- Practice-tailored training for general practitioners (GPs) increased the provision of quit-smoking advices (difference 0.56 advice per day; 95% CI 0.13,0.98) and the ability and intention of providing smoking cessation care. However, no effect on GPs' arrangement of follow-up, smokers' intention to quit, and long-term quit rates
- Institution-wide training programme for HIV care physicians in smoking cessation counselling led to increased smoking cessation and fewer relapses in HIV patients
- Targeted efforts to educate and support primary care physicians may improve physician adherence to smoking-cessation practice guidelines and smoking outcomes

- Practical training program to train pharmacists to give smoking cessation instructions increase significantly the confidence to give such instructions
- Training nurses how to deliver tobacco cessation interventions increases delivery of cessation services

Conclusion

Effectiveness

There was substantial fair to good level of retrievable evidence to suggest that quit smoking interventions comprising of pharmacotherapy (varenicline, NRT, bupropion), group behavioural support, phone counselling and text messaging were effective in reducing smoking rates in specific population and treatment settings. There was only limited fair level of retrievable evidence that suggest complementary and alternative methods and web-based methods were effective in promoting quit smoking

Safety

There was substantial good level of retrievable evidence to suggest that quit smoking intervention especially pharmacological therapy was safe in reducing smoking rates among various populations. The side-effects were reported to be mild and tolerable.

Economic evaluation

There was substantial good level of retrievable evidence that found nation-wide quit smoking campaigns, pharmacotherapy, telephone counselling, stop smoking clinics, hospital initiated interventions were cost-effective when used in specific population in the world

Organizational issues

There was fair level of retrievable evidence that suggest quit smoking intervention to be feasible, acceptable and adaptable by patients as well as by the healthcare providers.

Recommendation

Based on the review, multicomponent interventions should be utilised to achieve greater long-term continuous smoking cessation. Treatment programme consisting of combination of behavioural and psychological strategies with pharmacotherapy (varenicline, bupropion SR and NRT) should be implemented.

More high quality research is needed on the effectiveness of nicotine vaccine, complementary and alternative therapy as well as on the direct comparisons between combinations and classes of drugs (such as cytisine versus varenicline or the use of combinations of pharmacotherapy and technological based therapy). In this era of technology, more high quality research is also needed on the different types of mobile telephone– and internet-based behavioural interventions for smoking cessation, including text messaging and smartphone applications, which have high potential applicability to the Malaysian population. Further research on the benefit and safety of cessation medications among pregnant women is warranted, including assessment of optimal dosage and treatment timing.

ABBREVIATIONS

AEs	adverse events
BENESCO	Benefits of Smoking Cessation on Outcomes
BCT	Behavioural change techniques
CASP	Critical Appraisal Skills Programme
CBT	cognitive behaviour therapy
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CDTQ	cut down to quit
COT	salivary cotinine
CrI	credible interval
CVD	cardiovascular disease
DALYs	disability adjusted life years
EBQI	evidence-based quality improvement
ENDS	electronic nicotine delivery systems
FCTC	Framework Convention on Tobacco Control
GP	general practitioner
ICER	incremental cost-effectiveness ratio
ITM	Integrated Telemedicine
ITT	intention-to-treat
IPC	interpersonal communication
JBI	Joanna Briggs Institute
KTSND	Kano Test for Social Nicotine Dependence
LYS	life years saved
MOH	Ministry of Health
MPP	multiple-point prevalence
NCD	Non Communicable Diseases
NicVAX®	Nicotine Vaccine 3'-AmNic-rEPA
NRT	nicotine replacement therapy
OR	odds ratio
OTC	over the counter
PCTs	primary care trusts
PHO	primary health organization
PPA	point prevalence abstinence
QALY	quality-adjusted life year
QFL	Quit for Life
RR	relative risk
SCC	smoking cessation counselling
SES	socio-economic status
SR	sustained release
SSSs	stop smoking services
TC	text-based condition
TTM	transtheoretical model
USD	United States Dollar
USM	Universiti Sains Malaysia
VA	Veterans Health Administration
VC	video-based condition
WHO	World Health Organization
WTP	willingness to pay
YLL	years of life lost

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HEALTH TECHNOLOGY ASSESSMENT

1 BACKGROUND

Smoking-related diseases such as cancer and cardiovascular disease are the main causes of premature death globally and in Malaysia particularly. Global estimates of about 6 million people worldwide die each year from causes attributed to smoking.[1] In Malaysia, it is estimated that one-fifth of disability adjusted life years (DALYs) and one-third of years of life lost (YLL) for Malaysians were due to smoking-related diseases.[2] Diseases related to smoking remain the top causes of death in Ministry of Health (MOH) hospitals, accounting for more than 15% of hospitalisations and 35% of in-hospital deaths.[2]

World Health Organization (WHO) reported an overall reduction in the prevalence of tobacco smoking among men in 125 (72%) countries and among women in 155 (87%) countries during the most recent decade (2000–10).[3] If these trends continue, there would be an estimated 1.1 billion current tobacco smokers in 2025.[3] According to the recent National Health and Morbidity Survey 2015, it was estimated that nearly five million Malaysians aged 15 years and above smoked.[4] The prevalence of current smoker was 22.8% with the highest percentage of smokers were among those aged 25 to 44 years. The proportion among males was reported to be 30 times higher compared to females [43.0%, 95% Confidence Interval (CI) 41.4,44.6 versus 1.4%, 95% CI 1.1,1.8].[4] The prevalence of male smokers had reduced slightly from 43.9% in 2011 while the prevalence among females had increased from 1.0% in 2011. More than half (52.3%) of the current smokers had made an attempt to quit smoking in the last 12 months of the study with only less than 10% visited a healthcare provider.[4]

World Health Organization aims to reduce the global burden of disease related to tobacco through WHO Framework Convention on Tobacco Control (FCTC) and its MPOWER strategy.[5] Malaysia's targets according to WHO FCTC as well as the Global Non Communicable Diseases (NCD) targets, is to reduce our smoking prevalence down to 15% by the year 2025, and less than 5% by year 2045.[6]

The WHO MPOWER strategy focuses on six key activities which include *monitoring* tobacco use and prevention policies, *protecting* people from tobacco smoke, *offering* help to quit tobacco use, to *warn* about the dangers of tobacco, *enforcing bans* on tobacco advertising, promotion and sponsorship and *raising taxes* on tobacco.[7] In offering help to quit tobacco use, smoking cessation services can be offered at various levels ranging from healthcare and public health avenues to non-health channels including mass and social media.[7] These include physician-led and pharmacist-led interventions, practice nurse-led services, hospital-based patient discharge education, popular media campaigns, quitline telephone-based services and even social media networking with reported success in reducing smoking rates.[8-13]

Since their inception in 1999, the NHS Stop Smoking Services (SSS) in the United Kingdom (UK) has been providing services to smokers who would like to quit smoking. Services were established by Primary Care Trusts (PCTs) and operated primarily in primary care settings delivering behavioural support

and providing access to stop smoking medications. An observational study was conducted to evaluate the long-term outcomes for NHS Stop Smoking Services (ELONS study) and it was found to be effective in helping smokers to quit smoking.[14] Among 3000 smokers attending SSSs in nine areas of England, 41.2% and 8% of them were biochemically validated as abstinent from smoking at four weeks and one year follow-up, respectively.[14] Varenicline and combination nicotine replacement therapy (NRT) were both used frequently and increased chances of quitting compared with a single NRT product. Smokers who received specialist one-to-one behavioural support were twice as likely to have remained abstinent than those who were seen by a general practitioner (GP) practice and pharmacy providers [odds ratio (OR) 2.3, 95% CI 1.2,4.6].[14] A meta-analysis conducted on 40 studies of randomised and quasi-randomised controlled trials found higher abstinence rates among those who received combination of pharmacotherapy and behavioural treatment compared to usual care or brief advice or less intensive behavioural support (RR 1.82, 95% CI 1.66, 2.00).[8] Another meta-analysis of five studies found that pharmacist-led interventions has higher abstinence rates in smokers compared with controls (RR 2.21, 95% CI 1.49, 3.29).[15]

In Malaysia, as of 31 December 2015, there are 486 quit-smoking clinics and 47 hospitals within the Ministry of Health facilities throughout the country that provide smoking cessation services including promotion, screening, counselling and pharmacotherapy services.[16] On average, around 15% to 17% of those who registered in these quit smoking clinics will eventually cease smoking. In 2005, National Poison Centre, Universiti Sains Malaysia (USM) launched a quitline service which is carried out by the pharmacists through the telephone, supported by an online system called "Smokefree-Online System" (SOS).[17] This system was developed to assist the providers in evaluating the status of smokers as well as in providing advice to them through step by step procedures In line with the MPOWER strategy, the existing smoking cessation services in Malaysia needs to be strengthened and expanded to involve the private hospitals, clinics and the community pharmacies.[7] Activities of screening on smoking in schools are to be strengthened through the school dental team and counseling to stop smoking by the school counselors. To date, many tobacco control measures have been undertaken in concert with the anti-tobacco media approach to promote awareness among the public about the harmful effect of tobacco through the national anti-smoking media campaign known as the "*Tak Nak Merokok*" or Say No Campaign. Therefore, a Health Technology Assessment (HTA) was requested by the Head of Tobacco Control Unit, Disease Control Division, Ministry of Health Malaysia to assess the effectiveness, safety and cost-effectiveness of various smoking cessation interventions in public and private sectors in increasing quit smoking rate.

2 TECHNICAL FEATURES

There are two types of clinical intervention depending on the intensity of intervention and level of service provided; brief clinical intervention and intensive clinical intervention.[18] The five major steps (5 A's) of brief intervention involves ***asking*** patients about their current smoking, ***advising*** them to stop, ***assessing*** their willingness to begin treatment to quit, offering ***assistance*** either by providing further advice, a referral to a specialist service or recommendation of or a prescription for pharmacotherapy or ***arranging*** a

follow up wherever it is appropriate.[18] The focus of this opportunistic advice is to increase smokers' motivation to quit in improving success rate of quitting.
Alternatively, another approach to help smokers to quit smoking according to the updated New Zealand Smoking Cessation Guidelines 2014, is the ABC approach; [19]

A = **A**sk about and document every person's smoking status
B = Give **B**rief advice to stop to every person who smokes
C = Strongly encourage every person who smokes to use **C**essation support (a combination of behavioural support and stop-smoking medicine works best) and offer to help them access it. Refer to, or provide, cessation support to everyone who accepts your offer.

Intensive clinical interventions could be provided by any suitably trained doctors and other health care providers who have the resources available to give intensive interventions and are appropriate for any tobacco user willing to participate in them.[18] This could be achieved by increasing the length of individual treatment sessions, the number of treatment sessions and specialized behavioural therapies. The components of an intensive tobacco dependence intervention include;

i. Assessments - whether tobacco users are willing to make a quit attempt using an intensive treatment programme or their level of dependence.
ii. Programme clinician - Multiple types of clinicians are effective and should be used including non-medical clinicians delivering additional counselling interventions.
iii. Programme intensity - session length should be longer than 10 minutes with frequency of four or more sessions.
iv. Programme format could either be individual or group counselling with optional use of telephone counselling, self-help materials and cessation web sites and follow up interventions should be scheduled.
v. Type of counselling and behavioural therapies - Counselling should include practical counselling (problem solving/skills training) and intra-treatment social support.
vi. Medication - every smoker should be offered medications endorsed by Clinical Practice Guidelines, except when contraindicated or for specific populations for which there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, and adolescents). Certain combinations of cessation medications as well as combining counselling and medication can increase abstinence rates.

Pharmacotherapy for smoking cessation are divided into nicotine based – e.g. NRT and non-nicotine based - e.g. varenicline, sustained release (SR) bupropion, and nortriptyline. These are all first-line FDA-approved medications for smoking cessation. The choice of a specific first-line pharmacotherapy should be guided by four main factors; efficacy, safety, suitability and cost.[20]

The NRT helps to reduce withdrawal symptoms associated with stopping smoking by replacing the nicotine from cigarettes. It is available as skin patches, chewing gum, inhalers/inhalators, oral mouth sprays, microtabs,

nasal sprays and lozenges, all of which deliver nicotine to the brain more quickly than from skin patches, but less rapidly than from smoking cigarettes. Nicotine gum is available in 2 mg and 4 mg (per piece) doses. The 2 mg gum is recommended for patients smoking less than 20 cigarettes per day, while the 4 mg gum is recommended for patients smoking 20 or more cigarettes per day. Generally, the gum should be used for up to 12 weeks with no more than 24 pieces/day.[20]

Nicotine patch is available as Niquitin® (21, 14 and 7 mg), and Nicorette® (25, 15 and 10 mg preparations). If smoking ten cigarettes or more a day, start with Step 1 (21 mg) and gradually move to step 2 (14 mg) after six weeks and then step 3 (7 mg) for two weeks, as directed on pack over ten weeks. If smoking less than ten cigarettes a day, start at Step 2 and follow the eight-week programme described on the pack. Nicorette®15 mg x eight weeks, then 10 mg x two weeks and finally 5 mg x two weeks. Clinicians should consider individualizing treatment based on specific patient characteristics such as previous experience with the patch, amount smoked, degree of addictiveness, etc. Finally, clinicians should consider starting treatment on a lower patch dose in patients smoking ten or fewer cigarettes per day. A nicotine inhaler is available in 4 mg/cartridge. A dose from the nicotine inhaler consists of a puff or inhalation. Each cartridge delivers 4 mg of nicotine over 80 inhalations with recommended dosage is six to 16 cartridges/day and recommended duration of therapy is up to six months.[20]

Nicotine lozenges are available in 2 mg and 4 mg preparations. Prescription should be according to number of cigarettes per day; 2 mg for smoker of less than 20 cigarettes/day or 4 mg for smoker of 20 or more cigarettes/day. The stepwise treatment for abrupt cessation starting from one lozenge 1-2 hourly with minimum of nine lozenge/day at Week 1-6 to one lozenge 4-8 hourly up to maximum 15 lozenge/day at week 10-12. Maximum duration for treatment is 24 wk. For gradual cessation, smokers are advised to use a lozenge when there is a strong urge to smoke, up to 15 lozenge/day. Lozenge should not be chewed or swallowed. The NRT products do not need a doctor's prescription as they are Group C medications under the Poisons Act 1952. Adverse effects from using NRT are related to the type of product, and include skin irritation from patches and irritation to the inside of the mouth from gum and lozenge.[20]

Monotherapy of NRT provides lower level of plasma nicotine as compared to that produced by cigarette smoking. While monotherapy has been shown to be effective in majority of smokers, others, especially those who are hard-to-treat, may require combination strategy. Effective combination of first-line medications are: Long-term (more than 14 weeks) nicotine patch with other NRT (gum and spray), nicotine patch with nicotine inhaler and nicotine patch with bupropion SR. The common combination is an NRT patch (which gives a regular background level of nicotine) with gum or a nasal spray (taken every now and then to top up the level of nicotine to ease sudden cravings). Combination of pharmacological agents with behavioural intervention have been found to increase the chances of successfully quitting.

Commercially available forms of NRT

Varenicline, a specific nicotine receptor partial agonist, may help people stop smoking by a combination of maintaining moderate levels of dopamine to counteract withdrawal symptoms (acting as an agonist) and reducing smoking satisfaction (acting as an antagonist). The recommended dose is 1 mg varenicline twice daily following a 1-week titration as follows: Days 1-3: 0.5 mg once daily; Days 4-7: 0.5 mg twice daily; Day 8-end of treatment: 1 mg twice daily. Patients who cannot tolerate adverse effects of varenicline may have the dose temporarily or permanently lowered to 0.5 mg twice daily. It is appropriate as a first-line pharmacotherapy for smoking cessation. The patient should set a date to stop smoking. Dosing should start 1-2 weeks before this date. Patients should be treated for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with 1 mg twice daily may be considered. Similar to the NRT products classified as Group C medications under the Poisons Act 1952, varenicline does not require a doctor's prescription.

The antidepressants bupropion and nortriptyline also aid long-term smoking cessation by reduces the severity of tobacco withdrawal symptoms. Evidence suggests that the mode of action of bupropion and nortriptyline is independent of their antidepressant effect and that they are of similar efficacy to nicotine replacement.[20] Patients being prescribed on bupropion SR should begin taking a dose of 150 mg in the morning for 3 days, then increase to 150 mg twice daily. Dosing at 150 mg twice a day should continue for 7-12 weeks following the quit date. Unlike nicotine replacement products, patients should begin bupropion SR treatment 1-2 weeks before they quit smoking and use it for at least seven weeks. The most common side effects reported by bupropion SR users were insomnia, headache and dry mouth.[20] Patients on Nortriptyline should start the medication at least 10 to 28 days before their quit date, initially 25 mg/day, then increase gradually to 75-100 mg/day over 10 days-5 weeks. The treatment should continue for a total of 12 weeks with dose being tapered at the end of treatment to avoid withdrawal symptoms. Common adverse effects reported by nortriptyline users include drowsiness and dry mouth.[20]

Cytisine, like varenicline, is a partial agonist of nicotinic acetylcholine receptors (nAChRs), with an affinity for the α4β2 receptor subtype. It is derived naturally from the seeds of the plant Cytisus laborinum L. (golden rain acacia).[21] Currently, the recommended course of treatment starts at one tablet every two hours (six in total per day) for one to three days, tapered gradually, with a scheduled quit date at day 5, and ending with one to two tablets daily by days 21-25. Optimal doses and duration of treatment, however, are yet undetermined because no human pharmacokinetic data have been published.[21]

There are a few nicotine vaccines currently being developed and researched but none is yet to be licensed for public use. The rationale for immunization against nicotine is to induce antibodies that bind nicotine in the blood, thereby preventing it from crossing the blood brain barrier. It is postulated that with less nicotine reaching the brain immediately after smoking, the vicious cycle between smoking and nicotine related gratification will be broken.[20]

There are many other complementary and alternative treatments options to assist in quit smoking such as mindfulness meditation, hypnosis, acupuncture or acupressure and aversive smoking.[22] Mindfulness meditation is a mind-body practice which cultivates abilities to maintain focused and clear attention, and develop increased awareness of the present which includes Mind-body practices include meditation (mantra meditation, mindfulness meditation, and others), qi gong, tai chi, and yoga. Acupuncture for smoking cessation involves stimulation of specific acupoints on the ear using needles or laser therapy while aversive smoking is a procedure defined as inhaling a puff of cigarette repeatedly every six seconds for three minutes for two to three times per session until the patient is unable to smoke. Hypnotherapy is defined as the induction of a state of receptive and attentive concentration which enables the individual to adhere to suggestions and strategies to quit smoking.[22]

3 POLICY QUESTION

Which quit smoking intervention can be used in Malaysia to increase its quit smoking rate?

4 OBJECTIVES

4.1 To determine the effectiveness of quit smoking interventions in increasing quit smoking rate
4.2 To determine the safety of quit smoking interventions
4.3 To determine the economic impacts of quit smoking interventions in increasing quit smoking rate
4.4 To assess the ethical, legal, and organizational issues related to quit smoking interventions

Research questions

i. Which quit smoking interventions are effective in increasing quit smoking rate?
ii. Are quit smoking interventions safe?
iii. What are the economic impacts of quit smoking intervention in increasing quit smoking rate?
iv. What are the ethical, legal, and organizational issues related to quit smoking interventions?

5 METHODS

5.1. Literature search strategy

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (up to 1st Quarter 2015), EBM Reviews-Cochrane Central Register of Controlled Trials (2005 to September 2016), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2015), EBM Reviews-Health Technology Assessment (3rd Quarter 2016), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2015). Parallel searches were run in PubMed and Embase. Limits were applied to the articles published from year 2000 onwards and to study designs using meta-analysis, systematic review, clinical trials, and observational studies only. The last search was run on 7 October 2016.

Additional articles were identified from reviewing the references of retrieved articles. Studies were selected based on inclusion and exclusion criteria. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) tool and The Cochrane Collaboration's tool for assessing risk of bias. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force.[23]

5.2. Study Selection

Based on the policy question the following inclusion and exclusion criteria were used:-

5.2.1. Inclusion criteria

Population Problems	Smokers Tobacco and tobacco related product
Intervention	i. Pharmacological interventions a) Nicotine replacement therapy e.g.nicotine gum, nicotine patch, nicotine nasal spray b) Non-nicotine e.g. varenicline, bupropion ii. Behavioural intervention iii. Traditional & Complementary Medicine – herbal (e.g. cytisine) iv. Laser treatment v. Hypnosis vi. Web-based application vii. Mobile application viii. Quitlines
Comparators	Current practice, no comparator
Outcomes	i. Effectiveness of quit smoking interventions e.g. a) Prevalence of smokers b) Quit rate/ Smoking cessation rate / Abstinence rate c) Number of cigarettes smoked ii. Health related quality of life iii. Morbidity and mortality iv. Safety of quit smoking interventions (adverse events) v. Economic impacts 1. Cost-effectiveness 2. Cost-benefit vi. Medicolegal implication e.g. regulate accessibility to NRT vii. Social implication e.g. smoking related poverty viii. Organizational issues e.g training to ensure uniformity of programme
Study designs	HTA reports, systematic review with meta-analysis, systematic review, randomised controlled trial (RCT), cohort, case-control, cross-sectional and economic evaluation studies
Setting	Hospitals/Health Clinics/ General practitioners Dental clinics Community pharmacists Schools
English full text articles	

5.2.2. Exclusion criteria

i. Animal study
ii. Narrative review
iii. Experimental study
iv. Non English full text articles

Based on the above inclusion and exclusion criteria, study selection were carried out independently by two reviewers. The titles and abstracts of all studies were assessed for the above eligibility criteria. If it was absolutely clear from the title and / or abstract that the study was not relevant, it was excluded. If it was unclear from the title and / or the abstract, the full text article was retrieved. Two reviewers assessed the content of the full text articles. Disagreement was resolved by discussion.

5.3. Critical Appraisal of Literature

Assessment of risk of bias in included studies

The methodological quality of all the relevant full text articles (systematic reviews, economic evaluation, cohort and case control studies) retrieved was assessed using the Critical Appraisal Skills Programme (CASP) tool by two reviewers.[24] For SR the criteria assessed include selection of studies, assessment of quality of included studies, heterogeneity of included studies. For RCT, The Cochrane Collaboration's tool was utilised with criteria assessed were randomisation, allocation concealment, blinding, explanation on loss to follow-up, and intention to treat analysis.[25] For non-randomised experimental studies, with and without control group, Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Quasi-Experimental and NIH Quality Assessment Tool for Before-After (Pre-Post studies) were utilised. [26-27] For cohort study, the criteria assessed were selection of the cohort, accurate measurement of exposure and outcome, confounding factors, follow-up adequacy and length. For case control study, the criteria assessed were selection of the cases and control, accurate measurement of exposure, blinding and confounding factors. For economic evaluation, the criteria assessed include comprehensive description of competing alternatives, effectiveness established, effects of intervention identified, measured and valued appropriately, relevant resources and health outcome costs identified, measured in appropriate units and valued credibly, discounting, incremental analysis of the consequences and costs of alternative performed and sensitivity analysis performed. The CASP checklist is as in Appendix 4. The Cochrane's Collaboration Tool is as in Appendix 5. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force (Appendix 1).[23]

5.4. Analysis and Synthesis of Evidence

5.4.1 Data extraction strategy

Data were extracted from the included studies by a reviewer using a pre-designed data extraction form (evidence table as shown in Appendix 6) and checked by another reviewer. Disagreements were resolved by discussion. Details on: (1) methods including study design, (2) study population characteristics including gender, age, disease groups (3) type of intervention, (4) comparators, (5) type of outcome measures including: a) effectiveness of interventions b) adverse events or complications related to intervention c) quality of life, d) functional outcome, e) hospitalisation, f) economic evaluation, and g) organizational issues were extracted. The extracted data were presented and discussed with the expert committee.

5.4.2 Methods of data synthesis

Data on the safety, efficacy and cost implication of using quit smoking interventions compared with conventional treatment were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

6 RESULTS

A total of 14,571 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R), EBM Reviews-Cochrane Database of Systematic Reviews (up to 1st Quarter 2015), EBM Reviews-Cochrane Central Register of Controlled Trials (2005 to September 2016), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2015), EBM Reviews-Health Technology Assessment (3rd Quarter 2016), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2015), PubMed and Embase. Seventeen were identified from references of retrieved articles. After removal of 6582 duplicates, 8006 titles were screened and 7172 were excluded. Subsequently, 834 potentially relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the full text articles, 128 full text articles were included and 706 full text articles were excluded. The articles were excluded due to irrelevant study design, irrelevant population, irrelevant intervention, and irrelevant outcome as well as those already included in the systematic reviews. The excluded articles are listed in Appendix 7.

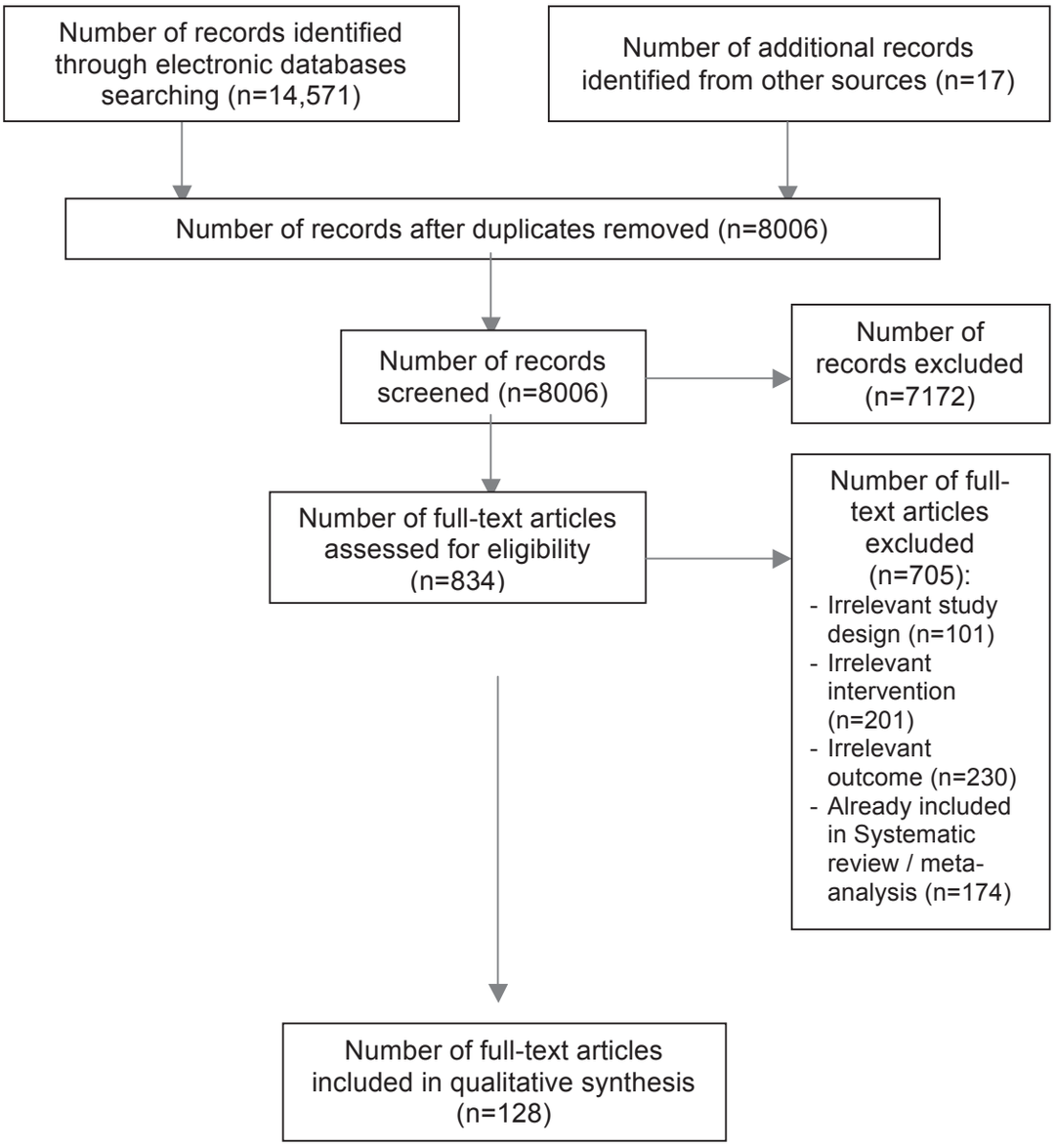

Figure 1: Flow chart of study selection

6.1. EFFECTIVENESS

Eighty eight articles (studies) related to the effectiveness of various programmes and methods in quit smoking which include; programmes in the population and hospitals, pharmacotherapy and complementary methods, behavioural, psychological, web-based methods, media, which met the inclusion criteria were included in this review. The articles were published between 2000 and 2016. The studies were conducted in the U.S.A., Netherland, Belgium, Italy, Turkey, Norway, Greece, Germany, United Kingdom, France, and Japan. Most of the studies were systematic review with meta-analysis and RCTs.

Assessment of Risk of Bias

Assessment of risk of bias of cohort (CASP)[24]

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Dobbie et al.[14]	+	+	+	?	+
Ashton, Rigby and Galletly[29]	?	+	+	+	+
Kotz et al.[32]	+	+	+	?	?
Alpert et al.[33]	+	+	+	+	+
Chang et al[39]	+	+	+	?	?
Richards et al.[43]	+	+	+	+	+
Shen et al[45]	+	+	+	?	?
Balmford et al.[47]	+	?	+	+	+
Yeo et al[105]	+	+	+	+	+
O'Connor et al[106]	+	+	+	+	+

Assessment of risk of bias of systematic review (CASP)[24]

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so? (heterogeneity)
Martin-Cantera et al.[28]	+	+	+	+
Brown, Platt and Amos[30]	+	+	+	-
Rosen et al.[34]	+	?	+	?
Papadakis et al.[36]	+	+	+	+
Bauld et al.[37]	+	+	+	+
Carr & Ebbert [44]	+	+	+	?
Saba et al[15]	+	+	+	?
Mojica et al[46]	+	?	+	?
Rabe et al[48]	+	+	+	?
Rigotti et al.[11]	+	+	+	?
Freund et al.[49]	+	+	+	+
Cahill et al.[51]	+	+	+	+
Stead et al.[52]	+	+	+	+

Hughes et al.[53]	+	+	+	+
Patnode et al[54]	+	+	+	-
Chang et al.[55]	+	+	+	+
David et al.[57]	+	+	+	+
Leaviss et al[58]	+	+	+	+
Cahill et al[59]	+	+	+	+
Hughes et al.[61]	+	+	+	+
Wang et al[62]	+	+	+	+
Kishi et al[64]	+	+	+	+
Van de Meer et al[65]	+	+	+	+
Nagrebetsky et al[66]	+	+	+	+
Nayan et al[67]	+	+	-	+
Eisenberg et al.[68]	+	+	-	+
Strassman et al.[69]	+	+	+	+
Coleman et al.[70]	+	+	+	+
Stanton & Grimshaw[72]	+	+	+	+
Patnode et al[73]	+	+	+	+
Chen & Wu[74]	+	+	+	+
Thomsen et al[75]	+	+	+	+
Ebbert, Elrashidi & Stead[77]	+	+	+	+
Barth et al.[79]	+	+	+	+
Stead, Lancaster, Koilpillai[80]	+	+	+	+
Lindson-Hawley et al[81]	+	+	+	+
Bartlett et al[82]	+	+	+	+
Bryant et al[83]	+	+	+	+
Bala & Lesniak[84]	+	+	+	+
Scott-Sheldon et al[85]	+	+	+	+
Whittaker et al[86]	+	+	+	+
Spohr et al.[89]	+	+	-	+
Park & Drake[91]	+	+	?	-
Lavender et al.[97]	+	+	+	+
Stead et al.[98]	+	+	+	+
Pan et al.[101]	+	+	+	+
Cahill et al.[104]	+	+	+	+
Tahiri, Mottillo & Joseph[109]	+	+	+	+

Barnes et al[110]	+	+	+	+
White et al[111]	+	+	+	?
Carim-Todd et al[112]	+	+	+	+

Assessment of risk of bias of RCT (Cochrane)[25]

Criteria assessed	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Fu et al.[31]	?	?	+	+	+	?
Yano et al[40]	?	-	+	?	?	+
Anthenelli et al[50]	+	-	+	+	?	+
Schnoll et al[56]	+	-	+	+	?	?
Hoogsteder et al.[60]	?	-	+	?	?	?
Smith et al[63]	?	?	+	+	+	?
Cooper et al[71]	+	?	+	+	+	+
Gilljam et al[76]	?	?	+	+	+	+
Severson et al[78]	?	?	+	?	+	?
Stanczyk et al[87]	?	?	+	+	+	+
Cheung et al.[90]	?	?	+	+	+	+
McDaniel et al[94]	?	?	+	+	+	+
Blebil et al[96]	?	?	+	+	+	?
Solomon et al[102]	?	?	+	+	+	+
Hasan et al[108]	?	?	+	+	+	+

Assessment of risk of bias of quasi experimental studies (non-RCT)[26]

Criteria assessed	Paone et al[38]	Miller et al[42]
Clear what is the cause and what is the effect?	+	+
Participants included in any comparisons similar?	?	+
Participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	?	+
Was there a control group?	+	+
Multiple measurements of outcome pre and post the intervention/ exposure?	+	+
Follow-up complete, and if not was follow-up adequately reported and strategies to deal with the loss to follow-up employed?	?	+

Outcomes of participants included in any comparisons measured in the same way?	+	?
Outcome measure in reliable way?	+	+
Appropriate statistical analysis used?	+	+

Assessment of risk of bias of pre-post studies with no control[27]

Criteria assessed	Shelley et al[41]	Bottorff et al[88]
Question or objective clearly stated?	+	+
Eligibility/selection criteria for study population clearly described?	+	+
Were participants representative for those who would be eligible for the test/ service/ intervention in the population of interest?	?	+
Were all eligible participants that met the prespecified entry criteria enrolled?	?	?
Sample size sufficiently large to provide confidence in findings?	?	+
Test/service/intervention clearly described and delivered consistently?	+	+
Outcome measures prespecified, valid, reliable, and assessed consistently?	+	+
People assessing the outcome measures blinded to participants exposure/ interventions?	-	?
Loss to follow-up after baseline 20% or less? Loss to follow-up accounted for in the analysis?	+	+
Statistical methods examine changes in outcome measures from before to after intervention? p value?	+	+
Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?	+	+
If intervention conducted at group level, did statistical analysis take into account of individual level data to determine effects at group level?	?	?

6.1.1. EFFECTIVENESS OF QUIT SMOKING PROGRAMMES

Twenty five articles (studies) related to the effectiveness of quit smoking programmes conducted in the community and four studies conducted in the hospitals were included in the review.

a. Community-based

Martin-Cantera et al. (2015) conducted a systematic review of randomised and nonrandomised controlled trials to evaluate multicomponent or complex primary care (PC) interventions for their effectiveness in continuous smoking abstinence by adult smokers. Out of 1147 references identified, nine studies were selected (10,204 participants, up to 48 months of follow-up, acceptable methodological quality). Methodologies used were mainly individual or group

sessions, telephone conversations, brochures or quit smoking kits, medications and economic incentives for doctors and no-cost medications for smokers. Complex interventions achieved long-term continuous abstinence ranging from 7% to 40%. Behavioural interventions were effective and had a dose–response effect. Both nicotine replacement and bupropion therapy were safe and effective, with no observed differences. Owing to the heterogeneity of interventions in the studies included, a meta-analysis was not conducted. The authors concluded that multicomponent/complex interventions in PC were effective and safe, appearing to achieve greater long-term continuous smoking cessation than usual care and counselling alone. Smoking interventions should include more than one component and a strong follow-up of the patient to maximise the results.[28,Level I]

Dobbie et al. (2015) evaluated long-term outcomes of nine NHS stop smoking services (SSSs) by conducting a prospective cohort study. The study explored the factors that determine longer-term abstinence from smoking following intervention by stop smoking services in England which were established by primary care trusts (PCTs) and operated primarily in primary care settings delivering behavioural support and providing access to NRT and bupropion. The outcome of the study was abstinence from smoking at four and 52 weeks after setting a quit date, validated by a carbon monoxide (CO) breath test. A total number of 3075 smokers were included in the prospective study with slightly more women setting quit dates than men, with 3.2% of clients pregnant at the time of study. One-quarter of the clients were under 30 years and one-quarter were aged more than 54 years. A combination of behavioural support and stop smoking medication delivered by SSS practitioners including primary care professionals who deliver 'brief interventions' (Level 1), community practitioners (nurses and health-care assistants, Level 2) and pharmacies (pharmacists to pharmacy assistants, Level 3) smoking cessation specialists(Level 4). Four in ten smokers (41%) recruited to the prospective study were biochemically validated as abstinent from smoking at four weeks. At the one-year follow-up, 8% of prospective study clients were CO validated as abstinent from smoking. Clients who received specialist one-to-one behavioural support were twice as likely to have remained abstinent versus seen by a general practitioner (GP) practice and pharmacy providers (OR 2.3, 95% CI 1.2, 4.6). Clients who received group behavioural support (either closed or rolling groups) were three times more likely to stop smoking versus seen by a GP practice or pharmacy providers (OR 3.4, 95% CI 1.7, 6.7). The satisfaction with services was high and well-being at baseline was found to be a predictor of abstinence from smoking at longer-term follow-up. Continued use of NRT at one year was rare, but no evidence of harm from longer-term use was identified. The authors concluded that SSSs in England was effective in helping smokers to quit smoking.[14, Level II-2]

Ashton, Rigby and Galletly (2015) conducted a cohort study to evaluate the effectiveness of a smoking cessation programme for smokers living with mental illness, provided within community mental health services, and determine factors which impact on the rates of cessation. One hundred and twenty nine smoking cessation group programmes were provided within community mental health services in South Australia between 2006 and 2011. Participants' smoking cessation rates were analysed in terms of demographic factors, smoking history, diagnosis and group participation. Participants completed written questionnaires at registration, at the end of each

programme and at 12 months. They were also asked to complete the Fagerström rating scale and use the Micro+Smokerlyzer to measure breath CO levels. Eight hundred and forty-four smokers living with mental illness registered for the programme. Many continued to be involved in addressing their tobacco use over more than one programme. At the end of their last programme, 581 completed an evaluation and 129 (22.2%) were not smoking. If it is assumed that all who did not complete an evaluation had continued smoking, then the cessation rate was 15.3%. Cessation rates were higher for those who attended more sessions, had decided at registration that they wanted to quit or had a lower level of nicotine dependence. Cessation rates were not significantly affected by gender, diagnosis or the number of years of smoking. The authors concluded that people with mental illness were concerned about their tobacco use and will seek help if this is available. Smoking cessation programmes which were tailored for this group of smokers can be effective and should be provided by mental health and tobacco control services.[29,Level II-2]

Brown, Platt and Amos (2014) conducted a systematic review to evaluate the equity impact of European individual-level smoking cessation interventions to reduce smoking in adults. Adults from lower socio-economic status (SES) groups are more likely to smoke and less likely to quit than adults from higher SES groups. Smoking cessation support is an important element of tobacco control; however, the equity impact of individual-level cessation support is uncertain. Equity impact was assessed as positive (reduced inequality), neutral (no difference by SES), negative (increased inequality) or unclear. Twenty-nine studies were included using different types of support: behavioural and pharmacological (17); behavioural only (11), including specialist (5), brief advice (1),mass media (2), text-based (1) and Internet-based (2); and pharmacological only (1). The distribution of equity effects on quitting was 10 neutral, 18 negative and one unclear. Two national studies of UK National Health Service (NHS) stop-smoking services showed overall positive equity impact on smoking prevalence. The evidence suggested that targeting low-SES smokers achieve a relatively higher service uptake among low-SES smokers, which can compensate for their lower quit rates. Untargeted smoking cessation interventions in Europe may have contributed to reducing adult smoking but are, on balance, likely to have increased inequalities in smoking. However, UK NHS stop-smoking services appear to reduce inequalities in smoking through increased relative reach through targeting services to low-SES smokers. The authors suggested more research to be done to strengthen the evidence-base for reducing smoking inequalities. [30, Level 1]

Fu et al. (2014) conducted the “Veterans Victory Over Tobacco Study”, a pragmatic randomised clinical trial involving a population-based registry of current smokers aged 18 to 80 years. A total of 6,400 current smokers, identified using the Department of Veterans Affairs (VA) electronic medical record, were randomised prior to contact to evaluate both the reach and effectiveness of the proactive care intervention. Current smokers were randomised to usual care or proactive care. Proactive care combined (1) proactive outreach and (2) offer of choice of smoking cessation services (telephone or in-person). Proactive outreach included mailed invitations followed by telephone outreach to motivate smokers to seek treatment with choice of services. Current tobacco use treatment approaches require smokers to request treatment or depend on the provider to initiate smoking

cessation care and are therefore reactive. Most smokers do not receive evidence-based treatments for tobacco use that include both behavioural counseling and pharmacotherapy. The primary outcome was 6-month prolonged smoking abstinence at one year and was assessed by a follow-up survey among all current smokers regardless of interest in quitting or treatment utilization. A total of 5123 participants were included in the primary analysis. The follow-up survey response rate was 66%. The population-level, 6-month prolonged smoking abstinence rate at one year was 13.5% for proactive care compared with 10.9% for usual care (p=0.02). Logistic regression mixed model analysis showed a significant effect of the proactive care intervention on six-month prolonged abstinence (OR 1.27, 95% CI 1.03,1.57). In analyses accounting for non-response using likelihood-based not-missing-at random models, the effect of proactive care on six months prolonged abstinence persisted (OR 1.33, 95% CI 1.17,1.51). The authors concluded that proactive, population-based tobacco cessation care using proactive outreach to connect smokers to evidence-based telephone or in-person smoking cessation services was effective for increasing long-term population-level cessation rates.[31,Level II-1]

Kotz et al. (2014) conducted a prospective cohort study of the effectiveness of varenicline versus NRT for smoking cessation in the “real world” when prescribed under routine circumstances and in the general population. The objective of the study was to use longitudinal data to compare the abstinence rates of smokers trying to stop having used varenicline versus NRT on prescription when provided with minimal professional support in the general population while adjusting for key potential confounders. Around 270 adults, who participated in a household survey, smoked at baseline, responded to the six months follow-up survey, and made at least one quit attempt between the two measurements with either varenicline or NRT treatment in their most recent quit attempt. The main outcome measure was self-reported abstinence up to the time of the survey, adjusted for key potential confounders including cigarette dependence (measured at baseline). Users of varenicline were younger, reported more time spent with urges to smoke at baseline, and were less likely to stop abruptly during their last quit attempt (all $p<0.05$). The adjusted odds of abstinence in users of varenicline were 3.83 (95% CI 1.88, 7.77) times higher compared with users of NRT treatment. The authors concluded that varenicline use with minimal professional support in the general population of smokers appears more effective than NRT treatment in achieving abstinence.[32,Level II-3]

Alpert et al. (2013) examined the population effectiveness of NRTs, either with or without professional counselling, and provide evidence needed to better inform health care coverage decisions. A prospective cohort study was conducted in three waves on a probability sample of 787 Massachusetts adult smokers who had recently quit smoking. The baseline response rate was 46%; follow-up was completed with 56% of the designated cohort at wave 2 and 68% at wave 3. The relationship between relapse to smoking at follow-up interviews and assistance used, including NRT with or without professional help, was examined. Almost one-third of recent quitters at each wave reported to have relapsed by the subsequent interview. Odds of relapse were unaffected by use of NRT for more than six weeks either with (p=0.117) or without (p=0.159) professional counselling and were highest among prior heavily dependent persons who reported NRT use for any length of time without professional counselling (OR 2.68). The study found that persons who

have quit smoking relapsed at equivalent rates, whether or not they used NRT to help them in their quit attempts. Cessation medication policy should be made in the larger context of public health, and increasing individual treatment coverage should not be at the expense of population evidence-based programmes and policies [33,Level II-3]

Rosen et al. (2012) conducted a systematic review and meta-analysis to quantify and assess the effectiveness of parental smoking cessation. Eighteen studies that targeted smoking parents of infants or young children, encouraged parents to quit smoking for their children's benefit, and measured parental quit rates were included. Interventions took place in hospitals, paediatric clinical settings, well-baby clinics, and family homes. Quit rates averaged 23.1% in the intervention group and 18.4% in the control group. The interventions successfully increased the parental quit rate. Subgroups with significant intervention benefits were children aged four to 17 years, interventions whose primary goal was cessation, interventions that offered medications, and interventions with high follow-up rates (80%). The authors concluded that interventions to achieve cessation among parents provide a worthwhile addition to the arsenal of cessation approaches. However, most parents do not quit, and additional strategies to protect children are needed. [34, Level 1]

Land et al. (2012) assessed the effect of systematic clinical interventions with cigarette smokers on quit status and the rates of smoking-related primary care office visits. The United States Public Health Service (USPHS) Guideline for Treating Tobacco Use and Dependence includes ten key recommendations regarding the identification and the treatment of tobacco users seen in all health care settings but the impact of system-wide brief interventions with cigarette smokers on smoking prevalence and health care utilization has not been examined using patient population-based data. Data on clinical interventions with cigarette smokers were examined for primary care office visits of 104,639 patients at 17 Harvard Vanguard Medical Associates (HVMA) sites. An operational definition of ''systems change'' was developed. It included thresholds for intervention frequency and sustainability. Twelve sites met the criteria. Five did not. Decreases in self-reported smoking prevalence were 40% greater at sites that achieved systems change (13.6% versus. 9.7%, p=0.01). On average, the likelihood of quitting increased by 2.6% (p=0.05, 95% CI: 0.1%, 4.6%) per occurrence of brief intervention. For patients with a recent history of current smoking whose home site experienced systems change, the likelihood of an office visit for smoking-related diagnoses decreased by 4.3% on an annualized basis after systems change occurred (p=0.05, 95% CI 0.5%, 8.1%). There was no change in the likelihood of an office visit for smoking-related diagnoses following systems change among non-smokers. The authors concluded that the clinical practice data from HVMA suggest that a systems approach can lead to significant reductions in smoking prevalence and the rate of office visits for smoking-related diseases. Most comprehensive tobacco intervention strategies focus on the provider or the tobacco user, but these results argue that health systems should be included as an integral component of a comprehensive tobacco intervention strategy. The HVMA results also give an indication of the potential health impacts when meaningful use of core tobacco measures are widely adopted. [35, Level II-3]

Papadakis et al. (2010) examined the strategies to increase the delivery of smoking cessation treatments in primary care settings by conducting a

systematic review and meta-analysis. The pooled OR was calculated for intervention group versus control group for practitioner performance for “5As” (Ask, Advise, Assess, Assist and Arrange) delivery and smoking abstinence. Multi-component interventions were defined as interventions which combined two or more intervention strategies. Thirty-seven trials met eligibility criteria. Evidence from multiple large-scale trials was found to support the efficacy of multi-component interventions in increasing “5As” delivery. The pooled OR for multicomponent interventions compared to control was 1.79 (95% CI 1.6, 2.1) for “ask”, 1.6 (95% CI 1.4,1.8) for “advice”, 9.3 (95% CI 6.8, 12.8) for “assist” (quit date) and 3.5 (95% CI 2.8, 4.2] for “assist” (prescribe medications). Evidence was also found to support the value of practice-level interventions in increasing 5As delivery. Adjunct counseling (OR 1.7, 95% CI 1.5, 2.0) and multi-component interventions (OR 2.2, 95% CI 1.7, 2.8) were found to significantly increase smoking abstinence. The authors found that multi-component interventions improve smoking outcomes in primary care settings. However future trials should attempt to isolate which components of multi-component interventions are required to optimize cost-effectiveness.[36, Level 1]

Bauld et al. (2010) conducted a systematic review to assess the effectiveness of intensive NHS smoking cessation services in helping smokers to quit. Twenty studies were included which suggested that intensive NHS treatments for smoking cessation were effective in helping smokers to quit. The national evaluation found 4-week CO monitoring validated quit rates of 53%, falling to 15% at one year. There is some evidence that group treatment may be more effective than one-to-one treatment, and the impact of ‘buddy support’ varies based on treatment type. Evidence on the effectiveness of in-patient interventions is currently very limited. Younger smokers, females, pregnant smokers and more deprived smokers appear to have lower short-term quit rates than other groups. However, further research is needed to determine the most effective models of NHS treatment for smoking cessation and the efficacy of those models with subgroups. Factors such as gender, age, socio-economic status and ethnicity appear to influence outcomes, but a current lack of diversity-specific analysis of results makes it impossible to ascertain the differential impact of intervention types on particular subpopulations.[37, Level 1]

Paone et al. (2008) assessed the combination of a smoking cessation programme with rehabilitation in improving stop-smoking rate. A parallel group study was performed during routine rehabilitation practice for outpatients. The study participants comprised an intervention group of 102 consecutive smokers who underwent a smoking cessation programme in a rehabilitation centre and a control group of 101 consecutive smokers who were referred to a smoking cessation centre in a pulmonary hospital. All participants underwent physical examination, pulmonary function tests and received identical behavioural and/or pharmacological treatment. In addition, the intervention group underwent rehabilitation practice three times a week for three months. The continuous abstinence rate at 12 months, which was validated by an expired air CO concentration of ten parts per million or less and a household interview, was 68% in the intervention group and 32% in the control group. Multivariable analysis showed that rehabilitation was significantly associated with smoking cessation after adjusting for years of smoking, number of cigarettes smoked, gender and treatment (OR=4.34, $p<0.001$). The study suggested that smoking cessation programmes during routine rehabilitation may be highly effective in helping smoking withdrawal

and should be a strongly recommended component of rehabilitation practice. [38, Level II-2]

Chang et al. (2008) studied the effects of a year 2005 increase in funding for smoking cessation services on provider participation, patient utilisation of smoking cessation services and cessation outcome at a six-month follow-up. The analyses are based on existing databases and on a follow-up study among smokers participating in the smoking cessation service. The effect of the policy is evaluated by comparing year 2004 (old policy) with year 2005 (new policy). The generalised estimating equations method was conducted to examine the effects of increasing funding for smoking cessation services on monthly smoking cessation services provided per physician and yearly consultations received per patient. Logistic regression was used to examine the effects of increasing funding on smoking cessation outcome. The study found the increased reimbursement rates and medication subsidies for smoking cessation to be positively related to the number of physicians enrolling in the programme (1841 in 2004 versus 3466 in 2005), the number of cessation consultations per month per physician (5.1 versus 14.6) and the number of cessation visits per year per patient (2.0 versus 2.5). Male providers and providers belonging to the private sector were found to offer more cessation consultations. The number of subjects receiving this counselling increased from 22 167 in 2004 to 109 508 in 2005. After adjusting for consumer and provider factors the likelihood of successful quitting among those counselled did not change. Overall, smokers who were older, had attempted to quit in the past year, had lower nicotine dependence, had gone to more smoking cessation service visits, had received consultations in the public sector and were seen by physicians delivering fewer consultations were more likely to have quit smoking at the six-month follow-up. Based on increases in physician enrolment and consultations and the increase in number of subjects receiving counselling and number of visits, the policy of increasing provider incentives and medication subsidies appeared to have successfully promoted smoking cessation services. [39, Level II-2]

Yano et al. (2008) evaluated the impact of a locally adapted evidence-based quality improvement (EBQI) approach to implementation of smoking cessation guidelines into routine practice. Patient questionnaires, practice surveys and administrative data in Veterans Health Administration (VA) primary care practices across five southwestern states were utilised. In a group-randomised trial of 18 VA facilities, matched on size and academic affiliation, intervention practices' abilities to implement evidence-based smoking cessation care following structured evidence review, local priority setting, quality improvement plan development, practice facilitation, expert feedback, and monitoring were evaluated. Control practices were received mailed guidelines and VA audit-feedback reports. To represent the population of primary care-based smokers, 36,445 patients were randomly sampled and screened to identify and enroll eligible smokers at baseline (N=51,941) and follow-up at 12 months (N=51,080). The authors used computer-assisted telephone interviewing to collect smoking behavior, nicotine dependence, readiness to change, health status, and patient sociodemographic. Practice surveys were used to measure structure and process changes and administrative data to assess population utilization patterns. The authors found that intervention practices adopted multifaceted EBQI plans, but had difficulty implementing them, ultimately focusing on smoking cessation clinic referral strategies. While attendance rates increased ($p<0.0001$), they found

no intervention effect on smoking cessation. In conclusion, EBQI stimulated practices to increase smoking cessation clinic referrals and try other less evidence-based interventions that did not translate into improved quit rates at a population level. [40, Level II-2]

Shelley et al. (2008) conducted a comparative analysis of policy approaches versus community-based smoking cessation intervention among Chinese immigrants living in New York City. A pre–post-test quasi-experimental design with representative samples from Chinese populations living in two communities in New York City: Flushing, Queens, the intervention community and Sunset Park, Brooklyn, the comparison community. From November 2002 to August 2003 baseline interviews were conducted with 2,537 adults aged 18–74 years. In early 2006, 1,384 participants from the original cohort completed the follow-up interview. During the intervention period (October 2003 to September 2005), both communities were exposed to tobacco control public policy changes. However, only Flushing received additional linguistically and culturally-specific community-level tobacco control interventions. The authors found that from 2002 to 2006 overall smoking prevalence among Chinese immigrants declined from 17.7% to 13.6%, a relative 23% decrease. After controlling for socio-demographic characteristics, there was an absolute 3.3% decrease in smoking prevalence attributed to policy changes with an additional absolute decline in prevalence of 2.8% in the intervention community relative to the control community. The authors concluded that city-wide tobacco control policies are effective among high-risk urban communities, such as Chinese immigrants. In addition, community-based tailored tobacco control interventions may increase the reduction in smoking prevalence rates beyond that achieved from public policies. [41, Level II-1]

Miller et al. (2005) assessed the effectiveness of a large-scale distribution programme of free nicotine patches in New York, after an increase in cigarette taxes and implementation of smoke-free workplace legislation. A six months follow-up survey was conducted to assess the success of this programme in improving smoking cessation on a population basis. A total of 34,090 eligible smokers who phoned a toll-free quitline were sent a six-week course of nicotine patches (two weeks each of 21 mg, 14 mg, and 7 mg per day). Brief follow-up counselling calls were also attempted. At six months after treatment, the smoking status of 1,305 randomly sampled NRT recipients and a non-randomly selected comparison group of eligible smokers who, because of mailing errors, did not receive the treatment were assessed. NRT recipients were compared with local survey-derived data for heavy smokers in New York City. An estimated 5% of all adults in New York City who smoked ten cigarettes or more daily received NRT; most recipients (64%) were non-white, foreign-born, or resided in a low-income neighbourhood. Of individuals contacted at six months, more NRT recipients than comparison group members successfully quit smoking (33% versus 6%, p=0.0001), and this difference remained significant after adjustment for demographic factors and amount smoked (OR 8.8, 95% CI 4.4, 17.8). Highest quit rates were associated with those who were foreign born (87 [39%]), older than 65 years (40 [47%]), and smoked less than 20 cigarettes per day (116 [35%]). Those who received a counselling call were more likely to stop smoking than those who did not (246 [38%] versus 189 [27%], p=0.001). With the conservative assumption that every six months follow-up survey non-respondent continued to smoke, the stop rate among NRT recipients was

20%. At least 6,038 successful quits were attributable to NRT receipt, and cost was USD 464 per quit. The authors concluded that easy access to cessation medication for diverse populations could help many more smokers to stop. [42, Level II-2]

Richards et al. (2003) conducted a prospective longitudinal cohort study to estimate programme utilisation and six months quit rates for enrolled patients in a general primary care setting which include a wide range of patient, practice and environmental variables to estimate any predictive effect on outcome. The 'Smokescreen' smoking cessation programme was introduced in Christchurch in 1995, with an initial study showing six months, self-reported quit rates of 10% and 17% (with a validated deception rate) in primary and secondary care settings. Substantial modifications were made to try to improve this rate in the primary care setting and the programme has been implemented widely. The NRT-based programme was implemented by Pegasus Health, an independent practitioner association (IPA) situated in the Christchurch urban area. A cohort of 516 patients enrolling in the programme over a two-month period was contacted six months after their nominated quit date. The main outcome measure was the six-month, self-reported quit rate. Of the 516 participants, 334 (65%) were contacted by mail or telephone. The overall six-month quit rate was 36% (95% CI 31, 41). Univariate analysis initially showed duration of NRT (p=0.03) and age band (p=0.004) were significant predictors of quitting, while living with a smoker (p=0.02), having made no previous quit attempts (p=0.02) and having heart disease (p=0.01) were all significant predictors of continued smoking at six months. Factors that did not predict whether respondents were smoking at six months included previous use of NRT, sex, ethnicity, who delivered the intervention, years of smoking, and cigarette dose. However, there was interaction between these factors as after multivariate analysis the only significant predictors of outcome were having others living in the house who smoked (OR 0.55, 95% CI 0.33, 0.93, p=0.03) and having made no previous quit attempts (OR 0.29, 95% CI 0.12, 0.71, p=0.02). Both these factors were significantly associated with continuing to smoke. The authors found that the programme compared favourably with six-month quit rates for NRT-based programmes reported in the international literature of 14–22%. The effectiveness of an NRT-based smoking cessation programme in a general primary care setting appears to have been significantly enhanced by local adaptation, the flexibility of a primary-care-team approach and subsidisation of NRT, together with facilitation responsive to individual practice needs. The success of this programme in helping individual patients quit, as well as its successful implementation in a wide primary care setting, suggests General Practice can play an important role in smoking cessation in a country with a high burden of disease from smoking-related illnesses. Widespread adoption of this kind of model in IPA/primary health organization (PHO) settings throughout New Zealand should be encouraged and supported. [43, Level II-2]

Carr and Ebbert (2006) assessed the effectiveness of interventions for tobacco cessation offered to cigarette smokers and smokeless tobacco users in the dental office or community setting. They included randomised and pseudo-randomised clinical trials assessing tobacco cessation interventions conducted by oral health professionals in the dental office or community setting with at least six months of follow up. Six clinical trials which assessed the efficacy of interventions in the dental office or a school community setting were finally included. All studies assessed the efficacy of interventions for

smokeless tobacco users, one of which included cigarettes smokers. All studies employed behavioural interventions and only one offered pharmacotherapy as an interventional component. All studies included an oral examination component. Pooling of the studies suggested that interventions conducted by oral health professionals increase tobacco abstinence rates (OR 1.44; 95% CI 1.16, 1.78) at 12 months or longer. Heterogeneity was evident (I^2 = 75%) and could not be adequately explained through subgroup or sensitivity analyses. The authors concluded that behavioural interventions for tobacco use conducted by oral health professionals incorporating an oral examination component in the dental office and community setting may increase tobacco abstinence rates among smokeless tobacco users. Differences between the studies limit the ability to make conclusive recommendations regarding the intervention components that should be incorporated into clinical practice.[44,Level I]

Shen et al. (2015) evaluated a pharmacist-assisted tobacco cessation programme that was conducted from 2004 to 2010, to identify participant- and pharmacy-specific factors associated with improved quit rates. To supplement data regarding participant characteristics and quit rates, semi structured interviews of seven participating pharmacists were conducted. Multivariate logistic regression quantified associations between successful abstinence at six months and participant characteristics and pharmacy-specific factors. Quit rates by pharmacy ranged from 1.1% to 59.4% (mean = 19.1%). There were 1235 participants enrolled at seven pharmacies, and because of missing participant data, 883 were included in the quantitative analysis. Three pharmacy-specific characteristics distinguished six months success rates: number and duration of follow-ups and format of counselling sessions. Participants followed up at least three times were more likely to quit at six months than those contacted once or twice (OR 4.9, 95% CI 1.6, 15.0). Compared with follow-ups of less than 15 minutes, longer durations of follow-ups were associated with higher success rates: 15 to 30 minutes (OR 7.2, 95% CI 3.7, 14.3); more than 30 minutes (OR 10.0, 95% CI 3.5,28.9). Participants who attended group sessions were more likely to quit at six months than those who attended individual sessions (OR 8.2, 95% CI 2.8, 23.9). Most pharmacists (88%) noted that participants' high or low commitment to quit was associated with success or failure, respectively. Several pharmacists (43%) noted difficulties with follow-up associated with participants' relapse. Time constraints were an obstacle noted by 70% of pharmacists. The authors concluded that pharmacy-specific factors, including counselling format and program intensity, affected the success of the cessation programme.[45,Level II-3]

Saba et al. (2014) conducted a meta-analysis of the effectiveness of smoking cessation interventions delivered by community pharmacists. The primary outcome of measure was smoking abstinence based on the 'most rigorous criterion'. Of the 1168 articles extracted, five studies (three RCTs and two controlled before-after studies) met the inclusion criteria, involving a total of 1426 smokers. Pharmacist interventions showed better abstinence rates as compared with controls (RR 2.21, 95% CI 1.49, 3.29). Compared with the control group, the RR (95% CI) in the intervention group was 3.21 (1.81, 5.72) for clinically validated abstinence and 1.66 (1.08–2.54) for self-reported abstinence. In the intervention group, the RR for short-term and long-term abstinence was 2.48(1.15,5.31) and 2.40(1.37,4.23), respectively. Pharmacist-led interventions can significantly impact abstinence rates in

smokers. Health policy makers should direct incentives for community pharmacists to provide such services.[15,Level I]

Mojica et al. (2004) evaluated smoking-cessation interventions by type of provider by conducting a meta-analysis. A random effects meta-regression was estimated to examine the effect of provider and whether the intervention contained NRT, on the intervention's relative risk of quitting as compared to placebo or usual care from studies published in databases from inception to 2000. Thirty additional studies not included in the previous 1996 and 2000 U.S. Public Health Service clinical practice guidelines were used to provide the most comprehensive analysis to date of the comparative effectiveness of different types of providers in interventions for smoking cessation that have been published. The effectiveness without NRT follows: psychologist (1.94, 95% CI 1.04,3.62); physician (1.87, 95% CI 1.42,2.45); counsellor (1.82, 95% CI 0.84,3.96); nurse (1.76, 95% CI 1.21,2.57); unknown (1.27, 95% CI 0.57, 2.82); other (1.18, 95% CI 0.67,2.10); and self-help (1.28, 95% CI 0.89,1.82). Effectiveness of most providers increased by almost two-fold with the use of NRT. The authors concluded that smoking-cessation interventions without NRT delivered by psychologists, physicians, or nurses were all effective. NRT increased the effectiveness of most providers.[46,Level I]

b. Hospital-based

Balmford et al. (2014) evaluated the implementation and effectiveness of a hospital based smoking cessation service in Germany in a cohort study. In the first two years of the service, 1432 patients were referred. Over half (55.3%) of counselled smokers agreed to participate in the study. Sustained abstinence for six months was achieved by 28.0% (missing cases coded as smokers), whereas seven-day point prevalence rates were between 30 and 35% at three, six and 12 months. Those who received more than four post-discharge calls were more likely to achieve sustained abstinence, as were older smokers, those with higher self-efficacy, and cardiovascular patients. The authors concluded that hospitalized patients in Germany were receptive to the offer of bedside counselling and to phone support post-discharge, and success rates are comparable to those achieved in other countries. They suggested strongly for the routine identification of smokers upon hospital admission, and the availability of cessation support both during hospitalization and following discharge. [47, Level II-3]

Rabe et al. (2013) evaluated the effectiveness of emergency department–initiated tobacco control (ETC) by conducting a systematic review and meta-analysis of RCTs. Point prevalence tobacco abstinence at one, three, six, and or 12-month follow-up was abstracted from each study. Seven studies with overall 1,986 participants were included. The strongest effect of ETC on point prevalence tobacco abstinence was found at one month: RR = 1.47 (three studies) (95% CI 1.06, 2.06), while the effect at three, six and 12 months was RR=1.24 (six studies) (95% CI 0.93,1.65); 1.13 (five studies) (95% CI 0.86,1.49); and 1.25 (one study) (95% CI 0.91,1.72), respectively. The benefit on combined point prevalence tobacco abstinence was RR=1.33 (seven studies) (95% CI 0.96,1.83), p=0.08 with RR = 1.33 (95% CI 0.92,1.92), p=0.10, for the five studies combining motivational interviewing and booster phone calls. ETC combining motivational interviewing and booster phone calls showed a trend toward increased episodically measured tobacco abstinence up to 12 months.[48,Level I]

Rigotti et al. (2012) studied the effectiveness of interventions for smoking cessation that are initiated for hospitalised patients in a systematic review. Randomized and quasi-randomised trials of behavioural, pharmacological or multicomponent interventions to help patients stop smoking, conducted with hospitalised patients who were current smokers or recent quitters (defined as having quit more than one month before hospital admission) were included. The intervention had to start in the hospital but could continue after hospital discharge. Both acute care hospitals and rehabilitation hospitals were included in this update, with separate analyses done for each type of hospital. Fifty trials met the inclusion criteria. Intensive counselling interventions that began during the hospital stay and continued with supportive contacts for at least one month after discharge increased smoking cessation rates after discharge (RR 1.37, 95% CI 1.27, 1.48; 25 trials). A specific benefit for post-discharge contact compared with usual care was found in a subset of trials in which all participants received a counselling intervention in the hospital and were randomly assigned to post-discharge contact or usual care. No statistically significant benefit was found for less intensive counselling interventions. Adding NRT to an intensive counselling intervention increased smoking cessation rates compared with intensive counselling alone (RR 1.54, 95% CI 1.34, 1.79, six trials). Adding varenicline to intensive counselling had a non-significant effect in two trials (RR 1.28, 95% CI 0.95,1.74). Adding bupropion did not produce a statistically significant increase in cessation over intensive counselling alone (RR 1.04, 95% CI 0.75,1.45, three trials). A similar pattern of results was observed in a subgroup of smokers admitted to hospital because of cardiovascular disease (CVD). In this subgroup, intensive intervention with follow-up support increased the rate of smoking cessation (RR 1.42, 95% CI 1.29,1.56), but less intensive interventions did not. One trial of intensive intervention including counselling and pharmacotherapy for smokers admitted with CVD assessed clinical and health care utilization endpoints, and found significant reductions in all-cause mortality and hospital readmission rates over a two-year follow-up period. These trials were all conducted in acute care hospitals. A comparable increase in smoking cessation rates was observed in a separate pooled analysis of intensive counselling interventions in rehabilitation hospitals (RR 1.71, 95% CI 1.37, 2.14, three trials).[11,Level I]

Freund et al. (2009) conducted a meta-analysis of intervention effectiveness in increasing smoking cessation care provision in hospitals. A review identified relevant studies published between 1994 and 2006. Intervention effectiveness in increasing smoking cessation care practices was examined for controlled studies using meta-analysis. Care practices examined were assessment of smoking status; advice to quit; counseling or assistance to quit; advising, offering, or providing NRT; and follow-up or referral. Of the 25 identified studies, 18 were U.S. based and in inpatient settings. Of the ten controlled trials, four addressed cardiac patients, five measured one smoking cessation care practice, and nine implemented multistrategic interventions (e.g., combining educational meetings with reminders and written resources). The methodology described in these studies was generally of poor quality. Meta-analysis of controlled trials demonstrated a significant intervention effect for provision of assistance and counseling to quit (pooled risk difference = 16.6, 95% CI 4.9,28.3) but not for assessment of smoking status, advice to quit, or the provision or discussion of NRT. Statistical heterogeneity was indicated for all smoking cessation care practices. An insufficient number of

studies precluded the use of meta-analysis for follow-up or referral for further assistance. The authors concluded that interventions can be effective in increasing the routine provision of hospital smoking cessation care while recommending future research to use more rigorous study design, to examine a broader range of smoking cessation care practices, and to focus on hospital-wide intervention implementation. [49, Level 1]

6.1.2. EFFECTIVENESS OF PHARMACOTHERAPY

Thirty articles (studies) related to the effectiveness of pharmacotherapy for quit smoking met the inclusion criteria and included in this review. They are of different populations – mental illness, chronic illnesses, young people, elderly, pregnant and postpartum ladies, pre-operative programmes and smokeless tobacco groups.

a. Non-specific groups

Anthenelli et al. (2016) compared the relative neuropsychiatric safety risk and efficacy of varenicline and bupropion with nicotine patch and placebo in smokers with and without psychiatric disorders. A randomised, double-blind, triple-dummy, placebo-controlled and active-controlled (nicotine patch; 21 mg per day with taper) trial of varenicline (1 mg twice a day) and bupropion (150 mg twice a day) for 12 weeks with 12-week non-treatment follow-up done at 140 centres (clinical trial centres, academic centres, and outpatient clinics) in 16 countries between Nov 30, 2011 and Jan 13, 2015. Participants were motivated-to-quit smokers with and without psychiatric disorders who received brief cessation counselling at each visit. The main efficacy endpoint was biochemically confirmed continuous abstinence for weeks 9–12. The primary endpoint was the incidence of a composite measure of moderate and severe neuropsychiatric adverse events. All participants randomly assigned were included in the efficacy analysis and those who received treatment were included in the safety analysis. A total of 8144 participants were randomly assigned, 4116 to the psychiatric cohort (4074 included in the safety analysis) and 4028 to the non-psychiatric cohort (3984 included in the safety analysis). Varenicline-treated participants achieved higher abstinence rates than those on placebo (OR 3.61, 95% CI 3.07, 4.24), nicotine patch (OR 1.68, 95% CI 1.46,1.93), and bupropion (OR 1.75, 95% CI 1.52, 2.01). Those on bupropion and nicotine patch achieved higher abstinence rates than those on placebo (OR 2.07, 95% CI 1.75,2.45) and (OR 2.15, 95% CI 1.82,2.54), respectively. Efficacy treatment comparison did not differ by cohort. The authors found that varenicline was more effective than placebo, nicotine patch, and bupropion in helping smokers achieve abstinence, whereas bupropion and nicotine patch were more effective than placebo. [50, Level I]

Cahill et al. (2016) studied the effectiveness of nicotine receptor partial agonists including varenicline and cytisine for smoking cessation in a systematic review. The study included RCTs which compared the treatment drug with placebo, comparisons with bupropion and nicotine patches where available. The main outcome measured was abstinence from smoking at longest follow-up using the most rigorous definition of abstinence, and preferred biochemically validated rates where they were reported. Two trials of cytisine (937 people) found that more participants taking cytisine stopped smoking compared with placebo at longest follow-up, with a pooled RR of 3.98 (95% CI 2.01,7.87; low-quality evidence). One recent trial comparing

cytisine with NRT in 1310 people found a benefit for cytisine at six months (RR 1.43, 95% CI 1.13,1.80).One trial of dianicline (602 people) failed to find evidence that it was effective (RR 1.20, 95% CI 0.82,1.75). However, this drug is no longer in development. A total of 39 trials were included that tested varenicline, 27 of which contributed to the primary analysis (varenicline versus placebo). Five of these trials also included a bupropion treatment arm. Eight trials compared varenicline with NRT. Nine studies tested variations in varenicline dosage, and 13 tested usage in disease-specific subgroups of patients. The included studies covered 25,290 participants, 11,801 of whom used varenicline. The pooled RR for continuous or sustained abstinence at six months or longer for varenicline at standard dosage versus placebo was 2.24 (95% CI 2.06,2.43; 27 trials, 12,625 people; high-quality evidence). Varenicline at lower or variable doses was also shown to be effective, with an RR of 2.08 (95% CI 1.56,2.78; four trials, 1266 people). The pooled RR for varenicline versus bupropion at six months was 1.39 (95% CI 1.25 to 1.54; 5 trials, 5877 people; high-quality evidence). The RR for varenicline versus NRT for abstinence at 24 weeks was 1.25 (95% CI 1.14 to 1.37; 8 trials, 6264 people; moderate-quality evidence). Four trials which tested the use of varenicline beyond the 12-week standard regimen found the drug to be well-tolerated during long-term use. The number needed to treat with varenicline for an additional beneficial outcome, based on the weighted mean control rate, is 11 (95% CI 9,13). The most commonly reported adverse effect of varenicline was nausea, which was mostly at mild to moderate levels and usually subsided overtime. There may be a 25% increase in the chance of serious adverse events (SAEs) among people using varenicline (RR 1.25; 95% CI 1.04,1.49; 29 trials, 15,370 people; high-quality evidence). These events include comorbidities such as infections, cancers and injuries, and most were considered by the trialists to be unrelated to the treatments. There is also evidence of higher losses to follow-up in the control groups compared with the intervention groups, leading to a likely under ascertainment of the true rate of SAEs among the controls. The authors concluded that cytisine increased the chances of quitting, although absolute quit rates were modest in two recent trials. Varenicline at standard dose increased the chances of successful long-term smoking cessation between two- and three-fold compared with pharmacologically unassisted quit attempts. Lower dose regimens also conferred benefits for cessation, while reducing the incidence of adverse events. More participants quit successfully with varenicline than with bupropion or with NRT. Limited evidence suggests that varenicline may have a role to play in relapse prevention. The most frequently recorded adverse effect of varenicline was nausea, but mostly at mild to moderate levels and tending to subside over time. Early reports of possible links to suicidal ideation and behaviour have not been confirmed by current research. Future trials of cytisine may test extended regimens and more intensive behavioural support.[51,Level 1]

In a systematic review with meta-analysis, Stead et al. (2016) assessed the effect of combining behavioural support and medication to aid smoking cessation, compared to a minimal intervention or usual care, and to identify whether there were different effects depending on characteristics of the treatment setting, intervention, population treated, or take-up of treatment. Randomised or quasi-randomised controlled trials evaluating combinations of pharmacotherapy and behavioural support for smoking cessation, compared to a control receiving usual care or brief advice or less intensive behavioural support were included. Trials recruiting only pregnant women, only

adolescents, and trials with less than six months follow-up were excluded. The main outcome measure was abstinence from smoking after at least six months of follow-up using biochemically validated rates if available. Fifty-three studies with a total of more than 25,000 participants met the inclusion criteria. A large proportion of studies recruited people in healthcare settings or with specific health needs. Most studies provided NRT. Behavioural support was typically provided by specialists in cessation counselling, who offered between four and eight contact sessions. The planned maximum duration of contact was typically more than 30 minutes but less than 300 minutes. Overall, studies were at low or unclear risk of bias, and findings were not sensitive to the exclusion of any of the six studies rated at high risk of bias in one domain. One large study (the Lung Health Study) contributed heterogeneity due to a substantially larger treatment effect than seen in other studies (RR 3.88, 95% CI 3.35,4.50). Since this study used a particularly intensive intervention which included extended availability of nicotine gum, multiple group sessions and long term maintenance and recycling contacts, the results may not be comparable with the interventions used in other studies, and hence it was not pooled in other analyses. Based on the remaining 52 studies (19,488 participants) there was high quality evidence (using GRADE) for a benefit of combined pharmacotherapy and behavioural treatment compared to usual care, brief advice or less intensive behavioural support (RR 1.83, 95% CI 1.68,1.98) with moderate statistical heterogeneity (I^2 = 36%).The pooled estimate for 43 trials that recruited participants in healthcare settings (RR 1.97, 95% CI 1.79,2.18) was higher than for eight trials with community-based recruitment (RR 1.53, 95% CI 1.33,1.76). Compared to the first version of the review, previous weak evidence of differences in other subgroup analyses has disappeared. The authors did not detect differences between subgroups defined by motivation to quit, treatment provider, number or duration of support sessions, or take-up of treatment. The authors concluded that interventions that combine pharmacotherapy and behavioural support increase smoking cessation success compared to a minimal intervention or usual care.[52,Level I]

Hughes et al. (2016) assessed the effect and safety of antidepressant medications to aid long-term smoking cessation. The medications include bupropion; doxepin; fluoxetine; imipramine; lazabemide; moclobemide; nortriptyline; paroxetine; S-Adenosyl-L-Methionine(SAMe); selegiline; sertraline; St. John's wort; tryptophan; venlafaxine; and zimeledine. Randomised trials comparing antidepressant medications to placebo or an alternative pharmacotherapy for smoking cessation were included. Trials comparing different doses, using pharmacotherapy to prevent relapse or re-initiate smoking cessation or to help smokers reduce cigarette consumption were also included. The main outcome measure was abstinence from smoking after at least six months follow-up in patients smoking at baseline, expressed as a RR. Twenty-four new trials were identified since the 2009 update, bringing the total number of included trials to 90. There were 65 trials of bupropion and ten trials of nortriptyline, with the majority at low or unclear risk of bias. There was high quality evidence that, when used as the sole pharmacotherapy, bupropion significantly increased long-term cessation (44 trials, N = 13,728, RR 1.62, 95% CI 1.49,1.76). There was moderate quality evidence, limited by a relatively small number of trials and participants, that nortriptyline also significantly increased long-term cessation when used as the sole pharmacotherapy (six trials, N=975, RR 2.03, 95% CI 1.48,2.78). There is insufficient evidence that adding bupropion (12 trials, N=3487, RR 1.19,

95% CI 0.94,1.51) or nortriptyline (four trials, N=1644, RR 1.21, 95% CI 0.94,1.55) to NRT provides an additional long-term benefit. Based on a limited amount of data from direct comparisons, bupropion and nortriptyline appear to be equally effective and of similar efficacy to NRT (bupropion versus nortriptyline three trials, N=417, RR 1.30, 95% CI 0.93,1.82; bupropion versus NRT eight trials, N=4096, RR 0.96, 95% CI 0.85,1.09; no direct comparisons between nortriptyline and NRT).Pooled results from four trials comparing bupropion to varenicline showed significantly lower quitting with bupropion than with varenicline (N=1810, RR 0.68, 95% CI 0.56,0.83). Meta-analyses did not detect a significant increase in the rate of serious adverse events amongst participants taking bupropion, though the CI only narrowly missed statistical significance (33 trials, N=9631, RR 1.30, 95% CI 1.00,1.69). There was a risk of about 1 in 1000 of seizures associated with bupropion use. Bupropion had been associated with suicide risk, but whether this was causal was unclear. Nortriptyline had the potential for serious side-effects, but none have been seen in the few small trials for smoking cessation. There was no evidence of a significant effect for selective serotonin reuptake inhibitors on their own (RR 0.93, 95% CI 0.71,1.22, N=1594; two trials fluoxetine, one trial paroxetine, one trial sertraline) or as an adjunct to NRT (three trials of fluoxetine, N=466, RR 0.70, 95% CI 0.64,1.82). Significant effects were also not detected for monoamine oxidase inhibitors (RR 1.29, 95% CI 0.93,1.79, N = 827; one trial moclobemide, five selegiline), the atypical antidepressant venlafaxine (one trial, N=147, RR 1.22, 95% CI 0.64,2.32), the herbal therapy St John's wort (hypericum) (two trials, N=261, RR 0.81, 95% CI 0.26, 2.53), or the dietary supplement SAMe (one trial, N =120, RR 0.70, 95% CI 0.24,2.07). The authors concluded that antidepressants bupropion and nortriptyline aid long-term smoking cessation. Adverse events with either medication appear to rarely be serious or lead to stopping medication. Evidence suggests that the mode of action of bupropion and nortriptyline is independent of their antidepressant effect and that they are of similar efficacy to nicotine replacement. Evidence also suggested that bupropion was less effective than varenicline, but further research is needed to confirm this finding. Evidence suggested that neither selective serotonin reuptake inhibitors (e.g. fluoxetine) nor monoamine oxidase inhibitors aided cessation.[53,Level I]

Patnode et al. (2015) conducted a systematic review and meta-analysis to assess the effectiveness and safety of pharmacotherapy and behavioural interventions for tobacco cessation. Five databases and eight organizational websites were searched for systematic reviews, and PubMed was searched through 1 March 2015 for trials on electronic nicotine delivery systems. Fifty four reviews were included. Behavioural interventions increased smoking cessation at six months or more (physician advice had a pooled RR of 1.76 (95% CI, 1.58,1.96). Nicotine replacement therapy (RR, 1.60 (95% CI 1.53,1.68), bupropion (RR 1.62, 95% CI 1.49,1.76), and varenicline (RR 2.27, 95% CI 2.02,2.55) were also effective for smoking cessation. Combined behavioural and pharmacotherapy interventions increased cessation by 82% compared with minimal intervention or usual care (RR 1.82, 95% CI 1.66,2.00). None of the drugs were associated with major cardiovascular adverse events. Only two trials addressed efficacy of electronic cigarettes for smoking cessation and found no benefit. Among pregnant women, behavioural interventions benefited cessation and perinatal health; effects of NRT were not significant. The authors concluded that behavioural and pharmacotherapy interventions improved rates of smoking cessation among

the general adult population, alone or in combination. Data on the effectiveness and safety of electronic nicotine delivery systems were limited.[54,Level I]

Chang et al. (2015) conducted a systematic review and meta-analysis of randomised controlled trials to investigate the efficacy and safety of varenicline combined with NRT. Three randomised controlled trials with 904 participants were included in the meta-analysis. All three were comparing combination therapy with varenicline therapy alone. The late outcomes were assessed in two of the three trials. Both the early and late outcomes were favourable for combination therapy (OR=1.50, 95% CI 1.14,1.97; OR=1.62, 95% CI 1.18,2.23, respectively). However, this significance diminished after eliminating a study with pre-cessation treatment using nicotine patch. The most common adverse events were nausea, insomnia, abnormal dreams, and headache. One study reported more skin reactions (14.4 % versus 7.8 %; p=0.03) associated with combination therapy. The authors concluded that combination therapy was more effective than varenicline alone, especially if pre-cessation treatment of nicotine patch is administrated. Adverse events of combination therapy were similar to mono-therapy except for skin reactions.[55,Level I]

Schnoll et al. (2015) compared eight (standard), 24 (extended), and 52 (maintenance) weeks of nicotine patch treatment for promoting tobacco abstinence in a RCT. The US Food and Drug Administration adopted labelling for nicotine patches to allow use beyond the standard 8 weeks. This decision was based in part on data showing increased efficacy for 24 weeks of treatment. Few studies have examined whether the use of nicotine patches beyond 24 weeks provides additional therapeutic benefit. The study recruited 525 treatment-seeking smokers for a RCT conducted from June 2009, through April 2014, through two universities. Smokers received 12 smoking cessation behavioural counselling sessions and were randomised to eight, 24, or 52 weeks of nicotine patch treatment. The primary outcome was seven-day point prevalence abstinence, confirmed with breath levels of CO at six and 12 months (intention to treat). At 24 weeks, 21.7% of participants in the standard treatment arm were abstinent, compared with 27.2% of participants in the extended and maintenance treatment arms (χ^2= 1.98; p=0.17). In a multivariate model controlled for covariates, participants in the extended and maintenance treatment arms reported significantly greater abstinence rates at 24 weeks compared with participants in the standard treatment arm (OR 1.70, 95% CI 1.03,2.81); p=0.04), had a longer duration of abstinence until relapse (β=21.30, 95% CI 10.30,32.25; p<0.001), reported smoking fewer cigarettes per day if not abstinent (mean [SD], 5.8 [5.3] versus 6.4 [5.1] cigarettes per day; β=0.43 (95% CI 0.06,0.82; p=0.02),and reported more abstinent days (mean [SD], 80.5 [38.1] versus 68.2 [43.7] days; (OR 1.55, 95% CI 1.06,2.26; p=0.02). At 52 weeks, participants in the maintenance treatment arm did not report significantly greater abstinence rates compared with participants in the standard and extended treatment arms (20.3% versus 23.8%; OR 1.17, 95% CI 0.69,1.98; p=0.57). Similarly, we found no difference in week 52 abstinence rates between participants in the extended and standard treatment arms (26.0% versus 21.7%; OR 1.33, 95% CI 0.72,2.45; p=0.36).Treatment duration was not associated with any adverse effects or adherence to the counselling regimen, but participants in the maintenance treatment arm reported lower adherence to the nicotine patch regimen compared with those in the standard and extended treatment arms (mean

[SD], 3.94 [2.5], 4.61 [2.0], and 4.7 [2.4] patches per week, respectively; $F_{2,522}$ =6.03; p =0.003). The findings supported the safety of long-term use of nicotine patch treatment, although they did not support efficacy beyond 24 weeks of treatment in a broad group of smokers.[56,Level I]

David et al. (2014) conducted a systematic review and meta-analysis to evaluate the efficacy of opioid antagonists in promoting long-term smoking cessation. Post-treatment abstinence was examined as a secondary outcome and effects on withdrawal symptoms, craving and reduced consumption were also explored. Participants included adult smokers with interventions of randomised trials comparing opioid antagonists to placebo or an alternative therapy for smoking cessation and reported data on abstinence for a minimum of 6 months. Outcomes included smoking abstinence at long-term follow-up (primary); abstinence at end of treatment (secondary); and effects on withdrawal, craving and smoking consumption (exploratory). Eight trials with a total of 1213 participants were included. Half of the trials examined the benefit of adding naltrexone versus placebo to NRT (NRT). There was no significant difference between naltrexone and placebo alone (RR 1.00; 95% CI 0.66,1.51) or as an adjunct to NRT (RR 0.95; 95% CI 0.70,1.30), with an overall pooled estimate of RR 0.97, 95% CI 0.76,1.24. Findings for naltrexone effects on withdrawal, craving and reduced smoking were equivocal. The findings indicated no beneficial effect of naltrexone alone or as an adjunct to NRT on short-term or long-term smoking abstinence. [57,Level I]

Leaviss et al. (2014) aimed to examine the clinical effectiveness and safety of cytisine from smoking cessation compared with varenicline as well as to develop an economic model to estimate the cost-effectiveness of cytisine and varenicline. The review included RCTs of adult smokers attempting to quit using varenicline or cytisine. Further interventions were considered (placebo, NRT, bupropion) to allow an indirect comparison between varenicline and cytisine. The primary outcome was abstinence at a minimum of six months' follow-up. Secondary outcomes were common adverse events such as abnormal dreams, headache, nausea, insomnia and serious adverse events. Twenty-three (RCTs) were included in the systematic review, comprising a total of 10,610 participants. Twenty-one trials of varenicline of differing dosing schedules and two trials of cytisine at standard dose met the inclusion criteria. No head-to-head trials comparing varenicline with cytisine were identified. The methodological quality of the studies was judged to be moderate to good. Cytisine was more efficacious than placebo [hazard ratio (HR) 4.27, 95% credible interval (CrI) 2.05,10.05], as was standard-dose varenicline (HR 2.58, 95% CrI 2.16,3.15). Standard-dose varenicline treatment was associated with significantly higher rates of headache, insomnia and nausea than placebo; there was no significant difference in the rates of abnormal dreams. There were no significant differences in the rates of headache or nausea between cytisine and placebo; data were identified for neither abnormal dreams nor insomnia. Using expected values, cytisine is anticipated to dominate varenicline, in that it produced more quality-adjusted life-years at a lower associated cost. This occurred in approximately 90% of the scenarios performed. However, owing to the large number of people who wish to quit smoking (estimated to be 3 million over a 10-year period), the implications of making an incorrect decision was large. The expected value of sample information indicated that conducting a head-to-head trial of cytisine and varenicline was worthwhile, and that 1000 smokers per arm was an appropriate number to recruit. On the basis of the evidence included in this

review, varenicline and cytisine are both effective interventions to aid smoking cessation when compared with placebo. Cytisine was estimated to be both more clinically effective and cost-effective than varenicline. However, there is uncertainty in the decision, and a head-to-head trial of cytisine and varenicline would appear to be an effective use of resources.[58,Level I]

Cahill et al. (2013) performed a systematic review and meta-analysis on pharmacologic treatment for smoking cessation. Participants were adult smokers, excluding reviews of smoking cessation for pregnant women and in particular disease groups or specific settings. The therapy covered were NRT, antidepressants (bupropion and nortriptyline), nicotine receptor partial agonists (varenicline and cytisine), anxiolytics, selective type 1 cannabinoid receptor antagonists (rimonabant), clonidine, lobeline, dianicline, mecamylamine, Nicobrevin, opioid antagonists, nicotine vaccines, and silver acetate. The outcome for benefit was continuous or prolonged abstinence at least six months from the start of treatment while outcome for harms was the incidence of serious adverse events associated with each of the treatments. For NRT, bupropion and varenicline, network meta-analyses were conducted, comparing each with the others and with placebo for benefit, and varenicline and bupropion for risks of serious adverse events. The authors identified 12 treatment-specific reviews. The analyses covered 267 studies, involving 101,804 participants. Both NRT and bupropion were superior to placebo (OR 1.84; 95% CrI 1.71,1.99, and 1.82; 95% CrI 1.60, 2.06 respectively). Varenicline increased the odds of quitting compared with placebo (OR 2.88, 95% CrI 2.40, 3.47). Head-to-head comparisons between bupropion and NRT showed equal efficacy (OR 0.99, 95% CrI 0.86,1.13). Varenicline was superior to single forms of NRT (OR 1.57, 95% CrI 1.29,1.91), and to bupropion (OR 1.59, 95% CrI 1.29, 1.96). It was more effective than nicotine patch (OR 1.51, 95% CrI 1.22, 1.87), than nicotine gum (OR 1.72, 95% CrI 1.38, 2.13), and than 'other' NRT (inhaler, spray, tablets, lozenges; OR 1.42, 95% CrI 1.12,1.79), but was not more effective than combination NRT (OR 1.06, 95% CrI 0.75, 1.48). Combination NRT also outperformed single formulations. The four types of NRT performed similarly against each other, apart from 'other' NRT, which was marginally more effective than NRT gum (OR 1.21, 95% CrI 1.01,1.46). Cytisine (a nicotine receptor partial agonist) returned positive findings (RR 3.98, 95% CI 2.01,7.87), without significant adverse events or SAEs. Across the 82 included and excluded bupropion trials, the estimate of six seizures in the bupropion arms versus none in the placebo arms was lower than the expected rate (1:1000), at about 1:1500. Meta-analysis of the bupropion studies demonstrated no excess of neuropsychiatric (RR 0.88, 95% CI 0.31, 2.50) or cardiovascular events (RR 0.77, 95% CI 0.37,1.59). Meta-analysis of 14 varenicline trials found no difference between the varenicline and placebo arms (RR 1.06, 95% CI 0.72,1.55), and subgroup analyses detected no significant excess of neuropsychiatric events (RR 0.53, 95% CI 0.17,1.67), or of cardiac events (RR 1.26; 95% CI 0.62, 2.56). Nortriptyline increased the chances of quitting (RR 2.03; 95% CI 1.48, 2.78). Neither nortriptyline nor bupropion were shown to enhance the effect of NRT compared with NRT alone. Clonidine increased the chances of quitting (RR 1.63, 95% CI 1.22, 2.18), but this was offset by a dose-dependent rise in adverse events. Mecamylamine in combination with NRT may increase the chances of quitting, but the current evidence is inconclusive. Other treatments failed to demonstrate a benefit compared with placebo. Nicotine vaccines were not yet licensed for use as an aid to smoking cessation or relapse prevention. Nicobrevin's UK license is now revoked, and

the manufacturers of rimonabant, taranabant and dianicline were no longer supporting the development or testing of these treatments. NRT, bupropion, varenicline and cytisine have been shown to improve the chances of quitting. Combination NRT and varenicline were equally effective as quitting aids. Nortriptyline also improves the chances of quitting. On current evidence, none of the treatments appear to have an incidence of adverse events that would mitigate their use. Further research is warranted into the safety of varenicline and into cytisine's potential as an effective and affordable treatment.[59,Level I]

Hoogsteder et al. examined the efficacy of adding Nicotine Vaccine 3'-AmNic-rEPA (NicVAX®) versus placebo to varenicline and behavioural support as an aid in smoking cessation and relapse prevention in a randomised placebo-controlled trial involving two research centres (Maastricht University Medical Centre and Slotervaart Hospital) in the Netherlands. A total of 558 smokers were assigned randomly to six injections with NicVAX® (n = 278) or placebo (n =280) both co-administered with open label varenicline and behavioural support. Outcomes were prolonged CO-validated abstinence from weeks nine to 52 (primary) and weeks 37 to 52 (secondary). They also performed a pre-planned subgroup analysis in the top 30% antibody responders. There was no difference in abstinence rates between NicVAX® and placebo from weeks nine to 52 [27.7 versus 30.0%, OR=0.89, 95% CI 0.62,1.29] or weeks 37 to 52 (33.8 versus 33.2%, OR 1.03, 95% CI 0.73,1.46). The top 30% antibody responders, compared to the placebo group, showed a non-significant tendency towards higher abstinence rates from weeks 37 to 52 (42.2% versus 33.2%, OR 1.47, 95% CI 0.89, 2.42). The authors concluded that the nicotine vaccine, NicVAX®, did not appear to improve the chances of stopping smoking when given in addition to varenicline and behavioural support.[60,Level I]

Hughes et al. (2011) assessed the effectiveness of over-the-counter (OTC) NRT in a qualitative review of non-randomised trials. Literature search via computer and other methods on (a) retrospective cohort studies of users versus non-users of OTC NRT and (b) studies of quit rates before versus after NRT went OTC or before versus after NRT was given free to quitline callers was conducted. The methods were too heterogeneous to allow meta-analysis. The results were similar for cohort and pre-versus post-studies. Most of the studies found numerically greater quitting among NRT users than nonusers. Often when NRT was not found effective, other assumed effective treatments (e.g., phone counseling) were also not found effective, suggesting biased or insensitive study methods. Only about half of the studies found statistically greater quitting among NRT users, and the most rigorous studies did not find greater quitting among users. Many studies found selection bias, for example, NRT users are more dependent smokers. The authors concluded that there were mixed results on the effectiveness of OTC NRT. Further secondary analyses using non-randomised comparisons are unlikely to resolve this issue due to sensitivity, specificity, and selection bias problems.[61,Level I]

Wang et al. (2008) evaluated "Cut down to quit" (CDTQ) with NRT in smoking cessation in a systematic review of effectiveness and economic analysis (a Health Technology Assessment report). A decision analytical model was constructed to estimate the cost-effectiveness of CDTQ from the NHS perspective. No systematic reviews of the effectiveness of CDTQ and no RCTs specifically addressing CDTQ were identified. Seven randomised placebo-controlled trials satisfied the inclusion criteria; six of these were

industry sponsored. However, sustained smoking cessation was only reported as a secondary outcome in these trials and required commencement of cessation within the first six weeks of treatment. Meta-analyses of the study level results demonstrated statistically significant superiority of NRT compared with placebo. Individual patient data from unpublished reports of five RCTs were used to calculate sustained abstinence of at least six months starting at any time during the treatment period (generally 12 months). From this meta-analysis indicated statistically significant superiority of NRT versus placebo (RR 2.06, 95% CI 1.34,3.15). The proportions achieving this outcome across all five RCTs were 6.75% of participants in receipt of NRT and 3.29% of those receiving placebo. The number-needed-to-treat was 29. This measure of sustained abstinence was used for economic modelling which will be described later in the cost-effectiveness of quit smoking intervention section. The authors concluded that NRT is an effective intervention in achieving sustained smoking abstinence for smokers who declare unwillingness or inability to attempt an abrupt quit. The 12-month sustained abstinence success rate in this population (approximately 5.3% with NRT versus approximately 2.6% with placebo) was considerably less than that documented for an abrupt quit NRT regime in smokers willing to attempt an abrupt quit with NRT (which according to other systematic reviews is around 16% with NRT versus 10% with placebo). Most of the evidence of effectiveness of CDTQ came from trials that required considerable patient–investigator contact. Therefore, for CDTQ with NRT to generate similar abstinence rates for this recalcitrant population in a real-world setting would probably require a similar mode of delivery. Randomised trials in recalcitrant smokers allowing head-to-head comparison of CDTQ delivered with various modalities would be informative.[62,Level I]

b. Mental illness patients

Smith et al. (2016) conducted a double-blind placebo controlled study in 87 schizophrenic smokers to evaluate the effects of varenicline (2 mg/day) on measures of smoking, cognition, psychiatric symptoms, and side-effects in schizophrenic patients who were cigarette smokers. Varenicline significantly decreased cotinine levels ($p<0.001$), and other objective and subjective measures of smoking ($p<0.01$), and responses on a smoking urges scale ($p= 0.02$), more than placebo. Varenicline did not improve scores on a cognitive battery (the Measurement and Treatment Research to Improve Cognition in Schizophrenia or MATRICS battery) designed to test the effect of drugs on cognitive performance in schizophrenia, either in overall MATRICS battery composite or individual domain scores, more than placebo. There were no significant differences between varenicline versus placebo effects on total symptom scores on psychiatric rating scales, Positive and Negative Symptom Scale (PANSS), Scale for Assessment of Negative Symptoms (SANS), or Calgary Depression scales ($\alpha=0.05$). Varenicline patients did not show greater side-effects than placebo treated patients at any time point when controlled for baseline side-effect scores. The study supports the use of varenicline as a safe drug for smoking reduction in schizophrenia but not as a cognitive enhancer.[63,Level I]

Kishi et al. (2015) performed an updated meta-analysis of randomised double-blind placebo-controlled trials (RCTs) on the effects of varenicline adjuvant therapy for smoking cessation in people with schizophrenia, on the basis of a previous meta-analysis (Tsoi in Cochrane Database Syst Rev

2:CD007253, 2013). Randomised controlled trials comparing varenicline adjuvant therapy with placebo in schizophrenia were included. Seven studies (total n = 439), including six with only schizophrenia (total n = 352), one with both schizophrenia (n=77) and bipolar disorder (n=10), were included. Varenicline was not superior to placebo in smoking cessation (RR=0.79, 95% CI 0.58,1.08, p=0.14, five RCTs, n=322). Varenicline failed to show its superiority to placebo for overall, positive, negative, and depressive symptoms. Moreover, there was no significant difference in the discontinuation rate due to all causes, clinical deterioration, or side effects between varenicline and placebo. Although varenicline caused less abnormal dreams/nightmares than placebo (RR=0.47, 95% CI 0.22,0.99, p=0.05, Number needed to harm [NNH]=not significant, four RCTs, n=288), it caused more nausea (RR 1.79, 95% CI 1.20,2.67, p=0.004, NNH=6, p=0.004, six RCTs, n=417). The study detected no significant difference in suicidal ideation and depression between varenicline and placebo. The results suggested that although varenicline adjuvant therapy was well tolerated, varenicline was not superior to placebo for smoking cessation in people with schizophrenia.[64,Level I]

Van de Meer et al. (2013) conducted a systematic review to evaluate the effectiveness of smoking cessation interventions, with and without specific mood management components, in smokers with current or past depression. Criteria for including studies in this review were that they had to be RCTs comparing smoking cessation interventions in adult smokers with current or past depression. Depression was defined as major depression or depressive symptoms. Studies where subgroups of participants with depression were identified, either pre-stated or post hoc was included. The outcome was abstinence from smoking after six months or longer follow-up. Subgroup analyses was also performed, by length of follow-up, depression measurement, depression group in study, antidepressant use, published or unpublished data, format of intervention, level of behavioural support, additional pharmacotherapy, type of antidepressant medication, and additional NRT. Forty nine RCTs were included of which 33 trials investigated smoking cessation interventions with specific mood management components for depression. In smokers with current depression, meta-analysis showed a significant positive effect for adding psychosocial mood management to a standard smoking cessation intervention when compared with standard smoking cessation intervention alone (11 trials, N=1844, RR 1.47, 95% CI 1.13,1.92). In smokers with past depression, there was a similar effect (13 trials, N=1496, RR 1.41, 95% CI 1.13,1.77). Meta-analysis resulted in a positive effect, although not significant, for adding bupropion compared with placebo in smokers with current depression (five trials, N=410, RR 1.37, 95% CI 0.83,2.27). There were not enough trial data to evaluate the effectiveness of fluoxetine and paroxetine for smokers with current depression. Bupropion (four trials, N=404, RR 2.04, 95% CI 1.31,3.18) might significantly increase long-term cessation among smokers with past depression when compared with placebo, but the evidence for bupropion is relatively weak due to the small number of studies and the post hoc subgroups for all the studies. There were not enough trial data to evaluate the effectiveness of fluoxetine, nortriptyline, paroxetine, selegiline, and sertraline in smokers with past depression. Twenty-three of the 49 trials investigated smoking cessation interventions without specific components for depression. There was heterogeneity between the trials which compared psychosocial interventions with standard smoking cessation counselling for both smokers with current

and past depression resulting the pooled effect not being estimated. One trial compared NRT versus placebo in smokers with current depression and found a positive, although not significant, effect (N=196, RR 2.64, 95% CI 0.93,7.45). Meta-analysis also found a positive, although not significant, effect for NRT versus placebo in smokers with past depression (three trials, N=432, RR 1.17, 95% CI 0.85,1.60). Three trials compared other pharmacotherapy versus placebo and six trials compared other interventions in smokers with current or past depression. The authors concluded that adding a psychosocial mood management component to a standard smoking cessation intervention increases long-term cessation rates in smokers with both current and past depression when compared with the standard intervention alone. Pooled results from four trials suggest that use of bupropion may increase long-term cessation in smokers with past depression. There was no evidence found for the use of bupropion in smokers with current depression. There was not enough evidence to evaluate the effectiveness of the other antidepressants in smokers with current or past depression. There was also not enough evidence to evaluate the group of trials that investigated interventions without specific mood management components for depression, including NRT and psychosocial interventions.[65,Level I]

c. Other medical illnesses

Nagrebetsky et al. (2014) evaluated the effects of more intensive smoking cessation interventions compared to less intensive interventions on smoking cessation in people with type 1 or type 2 diabetes in a systematic review and meta-analysis of RCTs. Interventions include smoking cessation interventions or medication (more intensive interventions) compared to usual care, counselling or optional medication (less intensive interventions). The primary outcome measures include biochemically verified smoking cessation while the secondary outcomes were adverse events and effects on glycaemic control. The authors also carried out a pooled analysis of self-reported smoking cessation outcomes. A total of 1783 citations and seven articles reporting eight trials in 872 participants were reviewed. All trials were of six months duration. Three trials included pharmacotherapy for smoking cessation. The risk ratio of biochemically verified smoking cessation was 1.32 (95% CI 0.23,7.43) for the more intensive interventions compared to less intensive interventions with significant heterogeneity (I^2=76%). Only one trial reported measures of glycaemic control. The authors concluded that there was an absence of evidence of efficacy for more intensive smoking cessation interventions in people with diabetes. The more intensive strategies tested in trials to date include interventions used in the general population, adding in diabetes-specific education about increased risk. Future research should focus on multicomponent smoking cessation interventions carried out over a period of at least 1 year, and also assess impact on glycaemic control.[66, Level I]

Nayan et al. (2013) examined the tobacco smoking cessation interventions and cessation rates in the oncology population through a systematic review and meta-analysis. Studies were included if they were RCTs or prospective cohort studies evaluating tobacco smoking cessation interventions with patients assigned to a usual care or an intervention group. The primary outcome measure was smoking cessation rates. The systematic review identified ten RCTs and three cohort studies. The therapeutic interventions included counselling, NRT, bupropion, and varenicline. Smoking cessation interventions had a pooled OR of 1.54 (95% CI 0.91,2.64) for patients in the

shorter follow-up group and 1.31 (95% CI 0.93,1.84) in the longer follow-up group. Smoking cessation interventions in the perioperative period had a pooled odds ratio of 2.31 (95% CI 1.32,4.07). The authors concluded that the tobacco cessation interventions in the oncology population, in both the short-term and long-term follow-up groups, do not significantly affect cessation rates. The perioperative period, though, may represent an important teachable moment with regard to smoking cessation.[67,Level I]

Eisenberg et al. (2010) conducted a meta-analysis of RCTs to compare the treatment effects of seven approved pharmacologic interventions for smoking cessation. They included studies that reported biochemically validated measures of abstinence at six and 12 months. A total of 70 published reports of 69 trials were identified, involving a total of 32,908 patients. Six of the seven pharmacotherapies studied were found to be more efficacious than placebo: varenicline (OR 2.41, 95%CrI 1.91,3.12), nicotine nasal spray (OR 2.37, 95% CrI 1.12,5.13), bupropion (OR 2.07, 95% CrI 1.73,2.55), transdermal nicotine (OR 2.07, 95%CrI 1.69,2.62), nicotine tablet (OR 2.06, 95%CrI 1.12,5.13) and nicotine gum (OR 1.71, 95% CrI 1.35,2.21). Similar results were obtained regardless of which measure of abstinence was used. Although the point estimate favoured nicotine inhaler over placebo (OR 2.17), these results were not conclusive because the interval included point of no difference (95% CrI 0.95,5.43). When all seven interventions were included in the same model, all were more efficacious than placebo. In the analysis of data from the varenicline trials that included bupropion control arms, varenicline was found to be superior to bupropion (OR 2.18, 95%CrI 1.09,4.08). Varenicline, bupropion and the five nicotine replacement therapies were all more efficacious than placebo at promoting smoking abstinence at six and 12 months.[68, Level I]

Strassman et al. (2009) aimed to rank order the effectiveness of smoking cessation interventions for chronic obstructive pulmonary disease (COPD) patients by conducting a network meta-analysis using logistic regression analyses to assess the comparative effectiveness of smoking cessation interventions while preserving randomisation of each trial. Ten databases were searched to identify randomised trials of smoking cessation counselling (SCC) with or without pharmacotherapy or NRT. The analysis of 7,372 COPD patients from six out of eight identified trials showed that SCC in combination with NRT had the greatest effect on prolonged abstinence rates versus usual care (OR 5.08, p<0.0001) versus SCC alone (2.80, p=0.001) and versus SCC combined with an antidepressant (1.53, p=0.28). The second most effective intervention was SCC combined with an antidepressant (3.32, p=0.002) versus SCC alone (1.83, p=0.007), with no difference between antidepressants. SCC alone was of borderline superiority compared with usual care (1.81, p=0.07). A small body of evidence suggested that SCC combined with NRT was more effective than other combinations and single smoking cessation treatments in COPD, but substantially more research is needed for this most important COPD treatment. [69,Level I]

d. Pregnant women

Coleman et al. (2015) examined the efficacy and safety of smoking cessation pharmacotherapies (including NRT, varenicline and bupropion), other medications, or electronic nicotine delivery systems (ENDS) for promoting smoking cessation during pregnancy. Randomised controlled trials conducted

in pregnant women with the following RCT designs are included; placebo-RCTs, any form of NRT, other pharmacotherapy, or ENDS, with or without behavioural support/cognitive behaviour therapy (CBT), or brief advice, compared with an identical placebo and behavioural support of similar intensity. Randomised Controlled Trials providing a comparison between i) any form of NRT, other pharmacotherapy, or ENDS added to behavioural support/CBT, or brief advice and ii) behavioural support of similar (ideally identical) intensity. Parallel- or cluster-randomised trials were eligible for inclusion. Quasi-randomised, cross-over and within-participant designs were not included due to the potential biases associated with these designs. The primary efficacy outcome was smoking cessation in later pregnancy (in all but one trial, at or around delivery); safety was assessed by 11 outcomes (principally birth outcomes) that indicated neonatal and infant well-being; as well as data on adherence with trial treatments. This review includes a total of nine trials which enrolled 2210 pregnant smokers: eight trials of NRT and one trial of bupropion as adjuncts to behavioural support/CBT. The risk of bias was generally low across trials. No trials were found investigating varenicline or ENDS. Compared to placebo and non-placebo controls, there was a difference in smoking rates observed in later pregnancy favouring use of NRT (RR 1.41, 95% CI 1.03,1.93, eight studies, 2199 women). However, subgroup analysis of placebo-RCTs provided a lower RR in favour of NRT (RR 1.28, 95% CI 0.99,1.66, five studies, 1926 women), whereas within the two non-placebo RCTs there was a strong positive effect of NRT, (RR 8.51, 95% CI 2.05,35.28, three studies, 273 women; p value for random effects subgroup interaction test = 0.01). There were no differences between NRT and control groups in rates of miscarriage, stillbirth, premature birth, birthweight, low birthweight, admissions to neonatal intensive care, caesarean section, congenital abnormalities or neonatal death. Compared to placebo group infants, at two years of age, infants born to women who had been randomised to NRT had higher rates of 'survival without developmental impairment' (one trial). Generally, adherence with trial NRT regimens was low. Non-serious side effects observed with NRT included headache, nausea and local reactions (e.g. skin irritation from patches or foul taste from gum), but these data could not be pooled. The authors concluded that NRT used in pregnancy for smoking cessation increases smoking cessation rates measured in late pregnancy by approximately 40%. There was evidence, suggesting that when potentially-biased, non-placebo RCTs were excluded from analyses, NRT was no more effective than placebo. There was no evidence that NRT used for smoking cessation in pregnancy has either positive or negative impacts on birth outcomes. However, evidence from the only trial to have followed up infants after birth, suggested use of NRT promotes healthy developmental outcomes in infants. Further research evidence on NRT efficacy and safety is needed, ideally from placebo-controlled RCTs which achieve higher adherence rates and which monitor infants' outcomes into childhood. Accruing data suggested that it would be ethical for future RCTs to investigate higher doses of NRT than those tested in the included studies.[70,Level I]

Cooper et al. (2014) conducted a randomised placebo-controlled, parallel-group trial (with economic evaluation) of NRT (The SNAP trial) in pregnancy to ascertain its clinical effectiveness and safety with follow-up at four weeks after randomisation, delivery and until infants were two years old. The authors hypothesized that NRT would increase smoking cessation in pregnancy without adversely affecting infants. Their objectives were to compare (1) at delivery, the clinical effectiveness and cost-effectiveness for achieving

biochemically validated smoking cessation of NRT patches with placebo patches in pregnancy and (2) in infants at two years of age, the effects of maternal NRT patch use with placebo patch use in pregnancy on behaviour, development and disability. Participants were among women between 12 and 24 weeks gestation who smoked more than ten cigarettes a day before and more than five during pregnancy, with an exhaled CO reading of more than 8 parts per million (p.p.m.). Interventions were either NRT patches (15 mg per 16 hours) or matched placebo as an 8-week course issued in two equal batches. A second batch was dispensed at four weeks to those abstinent from smoking. The main outcome measures in mothers included self-reported, prolonged abstinence from smoking between a quit date and childbirth, validated at delivery by CO measurement and/or salivary cotinine (COT) (primary outcome) as well as in infants at two years were absence of impairment, defined as no disability or problems with behavior and development. In terms of economic evaluation, the outcome measure was cost per 'quitter'. One thousand and fifty women enrolled (521 NRT, 529 placebo) in the study. There were 1,010 live singleton births and 12 participants had live twins, while there were 14 fetal deaths and no birth data for 14 participants. Numbers of adverse pregnancy and birth outcomes were similar in trial groups, except for a greater number of caesarean deliveries in the NRT group. All participants were included in the intention-to-treat (ITT) analyses; those lost to follow-up (7% for primary outcome) were assumed to be smoking. At one month after randomisation, the validated cessation rate was higher in the NRT group (21.3% versus 11.7%) with OR (95% CI) for cessation with NRT was 2.05 (1.46,2.88). At delivery, there was no difference between groups' smoking cessation rates: 9.4% in the NRT and 7.6% in the placebo group [OR (95% CI), 1.26 (0.82, 1.96)]. Infants: at two years, analyses were based on data from 888 out of 1010 (87.9%) singleton infants (including four postnatal infant deaths) [445/503 (88.5%) NRT, 443/507 (87.4%) placebo] and used multiple imputation. In the NRT group, 72.6% (323/445) had no impairment compared with 65.5% (290/443) in placebo (OR 1.40, 95% CI 1.05,1.86). The incremental cost-effectiveness ratio for NRT use was £4156 per quitter (£4926 including twins), but there was substantial uncertainty around these estimates. The authors concluded that NRT patches had no enduring, significant effect on smoking in pregnancy and two-year-olds born to women who used NRT were more likely to have survived without any developmental impairment. Further studies should investigate the clinical effectiveness and safety of higher doses of NRT.[71,Level I]

e. Young people

Stanton and Grimshaw (2013) conducted systematic review and meta-analysis to evaluate the effectiveness of strategies that help young people to stop smoking tobacco. This is the second update of a Cochrane review first published in 2006. Randomized controlled trials, cluster-randomised controlled trials and other controlled trials recruiting young people, aged less than 20, who were regular tobacco smokers were included. Any study interventions including pharmacotherapy, psycho-social interventions and complex programmes targeting families, schools or communities were selected. Exclusion criteria include programmes primarily aimed at prevention of uptake. The primary outcome was smoking status after at least six months follow-up among those who smoked at baseline. Twenty-eight trials involving approximately 6000 young people met our inclusion criteria (12 cluster-randomised controlled trials, 14 randomised controlled trials and two

controlled trials). The majority of studies were judged to be at high or unclear risk of bias in at least one domain. Many studies combined components from various theoretical backgrounds to form complex interventions. The majority used some form of motivational enhancement combined with psychological support such as cognitive behavioural therapy (CBT) and some were tailored to stage of change using the transtheoretical model (TTM). Three trials based mainly on TTM interventions achieved moderate long-term success, with a pooled RR of 1.56 at one year (95% CI 1.21,2.01). The 12 trials that included some form of motivational enhancement gave an estimated RR of 1.60 (95% CI 1.28,2.01). None of the 13 individual trials of complex interventions that included cognitive behavioural therapy achieved statistically significant results, and results were not pooled due to clinical heterogeneity. There was a marginally significant effect of pooling six studies of the Not on Tobacco programme (RR of 1.31, 95% CI 1.01,1.71), although three of the trials used abstinence for as little as 24 hours at six months as the cessation outcome. A small trial testing NRT did not detect a statistically significant effect. Two trials of bupropion, one testing two doses and one testing it as an adjunct to NRT, did not detect significant effects. Studies of pharmacotherapies reported some adverse events considered related to study treatment, though most were mild, whereas no adverse events were reported in studies of behavioural interventions. The authors concluded that multicomponent approaches show promise, with some persistence of abstinence (30 days point prevalence abstinence or continuous abstinence at six months), especially those incorporating elements sensitive to stage of change and using motivational enhancement and CBT. Given the episodic nature of adolescent smoking, more data is needed on sustained quitting. There were few trials with evidence about pharmacological interventions (nicotine replacement and bupropion), and none demonstrated effectiveness for adolescent smokers. There is not yet sufficient evidence to recommend widespread implementation of any one model. There continues to be a need for well-designed adequately powered randomised controlled trials of interventions for this population of smokers.[72, Level 1]

Patnode et al. (2013) reviewed the evidence for the efficacy and harms of primary care-relevant interventions that aim to reduce tobacco use among children and adolescents. Trials of behaviour-based or medication interventions that were relevant to primary care and reported tobacco use, health outcomes, or harms were included. Nineteen trials (four good-quality and 15 fair-quality) that were designed to prevent tobacco use initiation or promote cessation (or both) and reported self-reported smoking status or harms were included. Pooled analyses from a random-effects meta-analysis suggested a 19% relative reduction (RR 0.81, 95% CI 0.70,0.93); absolute risk difference, -0.02 (95% CI -0.03,0.00) in smoking initiation among participants in behaviour-based prevention interventions compared with control participants. Neither behaviour-based nor bupropion cessation interventions improved cessation rates. Findings about the harms related to bupropion use were mixed. No studies reported health outcomes. Interventions and measures were heterogeneous. Most trials examined only cigarette smoking. Authors concluded that primary care-relevant interventions may prevent smoking initiation over 12 months in children and adolescents.[73, Level I]

f. Elderly

Chen and Wu (2015) conducted a systematic review and meta-analysis to quantitatively assess the efficacy cessation interventions for smokers aged more than 50 years. Twenty-nine randomised clinical trials met the inclusion criteria. Three main types of interventions were identified. Fixed-effects analysis showed significant treatment effects for pharmacological (RR = 3.18, 95% CI 1.89,5.36), non-pharmacological (RR = 1.80, 95% CI 1.67,1.94), and multimodal interventions (RR = 1.61,95% CI 1.41,1.84) compared with control group. Estimations based on meta-regression suggested that pharmacological intervention (mean point prevalence abstinence rate (PPA) = 26.10%, 95% CI 15.20,37.00) resembled non-pharmacological (27.97%, 95% CI 24.00,31.94), and multimodal interventions (36.64%, 95% CI 31.66,41.62); and non-pharmacological and multimodal interventions had higher PPAs than the control group (18.80%, 95% CI 14.48,23.12), after adjusting for a number of trial and sample characteristics. The authors found that only a small number of smoking cessation studies examined smokers aged more than 50 years. Additional research is recommended to determine smoking cessation efficacy for diverse older population groups (e.g., ethnic minorities).[74,Level I]

g. Pre-operative patients

Thomsen et al. (2014) assessed the effect of preoperative smoking intervention on smoking cessation at the time of surgery and 12 months post operatively, and on the incidence of postoperative complications in a systematic review. Randomized controlled trials that recruited people who smoked prior to surgery, offered a smoking cessation intervention, and measured preoperative and long-term abstinence from smoking or the incidence of postoperative complications or both outcomes were included in the review. Thirteen trials enrolling 2,010 participants met the inclusion criteria. One trial did not report cessation as an outcome. Seven reported some measure of postoperative morbidity. Most studies were judged to be at low risk of bias but the overall quality of evidence was moderate due to the small number of studies contributing to each comparison. The authors' concluded that there is evidence that preoperative smoking interventions providing behavioural support and offering NRT increase short-term smoking cessation and may reduce postoperative morbidity. One trial of varenicline begun shortly before surgery has shown a benefit on long-term cessation but did not detect an effect on early abstinence or on postoperative complications. The optimal preoperative intervention intensity remains unknown. Based on indirect comparisons and evidence from two small trials, interventions that begin four to eight weeks before surgery, include weekly counselling and use NRT are more likely to have an impact on complications and on long-term smoking cessation.[75,Level I]

Gilljam et al. (2009) evaluated how smoking cessation intervention initiated four weeks prior to elective surgery affects the probability of permanent cessation. They randomly assigned 117 patients, scheduled to undergo elective orthopaedic and general surgery, to smoking cessation intervention and control group. The intervention group underwent a programme initiated, on average, four weeks prior to surgery with weekly meetings or telephone counselling and were provided with free NRT. The control group received standard care. As a result, 20 out of 55 (36%) patients in the intervention group versus 1 out of 62 (2%) in the control group became completely abstinent throughout the peri-operative period ($p < 0.001$). After one year,

those in the intervention group was most likely to be abstinent (18/55 (33%) versus 9/62 (15%) of the controls (p = 0.03). Level of nicotine dependence and obesity seemed to be a predictor of long-term abstinence (p = 0.02).[76,Level]

h. Smokeless tobacco users

Ebbert, Elrashidi and Stead (2015) conducted systematic review to assess the effects of behavioural and pharmacologic interventions for the treatment of smokeless tobacco (ST) use. Randomized trials of behavioural or pharmacological interventions to help users of ST to quit with follow-up of at least six months. For subgroups of trials with similar types of intervention and without substantial statistical heterogeneity, pooled effects using a Mantel-Haenszel fixed-effect method was estimated. Thirty four trials that met the inclusion criteria were selected, of which nine were new for the update, representing over 16,000 participants. There was moderate quality evidence from two studies suggesting that varenicline increases ST abstinence rates (RR 1.34, 95% CI 1.08,1.68, 507 participants). Pooled results from two trials of bupropion did not detect a benefit of treatment at six months or longer (RR 0.89, 95% CI 0.54 ,1.44, 293 participants) but the CI was wide. Neither nicotine patch (five trials, RR 1.13, 95% CI 0.93,1.37, 1083 participants) nor nicotine gum (two trials, RR 0.99, 95% CI 0.68,1.43, 310 participants) increased abstinence. Pooling five studies of nicotine lozenges did increase tobacco abstinence (RR 1.36, 95% CI 1.17,1.59, 1529 participants) but confidence in this estimate is low as the result is sensitive to the exclusion of three trials which did not use a placebo control. Statistical heterogeneity was evident among the 17 trials of behavioural interventions: eight of them reported statistically and clinically significant benefits; six suggested benefit but with wide CIs and no statistical significance; and three had similar intervention and control quit rates and relatively narrow CIs. Heterogeneity was not explained by study design (individual or cluster randomization), whether participants were selected for interest in quitting, or specific intervention components. In a post hoc subgroup analysis, trials of behavioural interventions incorporating telephone support, with or without oral examination and feedback, were associated with larger effect sizes, but oral examination and feedback alone were not associated with benefit. In one trial an interactive website increased abstinence more than a static website. One trial comparing immediate cessation using nicotine patch versus a reduction approach using either nicotine lozenge or brand switching showed greater success for the abrupt cessation group. The authors concluded that varenicline, nicotine lozenges and behavioural interventions may help ST users to quit. Confidence in results for nicotine lozenges is limited. Confidence in the size of effect from behavioural interventions is limited because the components of behavioural interventions that contribute to their impact are not clear.[77,Level I]

Severson et al. (2015) conducted a randomised controlled trial of nicotine lozenges versus phone counselling for smokeless tobacco cessation. The authors recruited smokeless tobacco (ST) users online (N = 1067) and randomly assigned them to one of 3 conditions:(a) a lozenge group (n = 356), who were mailed 4-mg nicotine lozenges; (b) a coach calls group (n = 354), who were offered 3 coaching phone calls; or (c) a lozenge plus coach calls group (N = 357), who received both lozenges and coaching calls. Additionally, all participants were mailed self-help materials. Self-reported tobacco abstinence was assessed at three and six months after randomization. Complete-case and intention-to-treat (ITT) analyses for all tobacco

abstinence were performed at three months, six months, and both three and six months (repeated point prevalence). ITT analyses revealed that the lozenge plus coach calls condition was significantly more successful in encouraging tobacco abstinence than either the lozenge group or the coach calls group, which did not differ. The authors concluded that combining nicotine lozenges and phone counseling significantly increased tobacco abstinence rates compared with either intervention alone, where as coach calls and lozenges were equivalent. The study confirms the high tobacco abstinence rates for self-help ST cessation interventions and offers guidance to providing tobacco treatment to ST users.[78,Level I]

6.1.3. EFFECTIVENESS OF PSYCHOLOGICAL AND BEHAVIOURAL INTERVENTIONS

Thirty articles (studies) related to the effectiveness of psychological and behavioural interventions for quit smoking met the inclusion criteria and included in this review. The interventions included were cognitive/behavioural interventions, technology-based methods, quitlines, incentives and self-help materials.

a. Cognitive/Behavioural Interventions

Barth et al. (2015) performed an update of a Cochrane review previously published in 2008. The review aimed to examine the efficacy of psychosocial interventions for smoking cessation in patients with coronary heart disease (CHD) in short-term (six to 12 month follow-up) and long-term (more than 12 months). Moderators of treatment effects (i.e. intervention types, treatment dose, methodological criteria) were used for stratification. Randomised controlled trials (RCTs) in patients with CHD with a minimum follow-up of six months were included. A total of 40 RCTs meeting inclusion criteria (21 trials were new in this update, 5 new trials contributed to long-term results (more than 12 months)). Interventions consisted of behavioural therapeutic approaches, telephone support and self-help material and were either focused on smoking cessation alone or addressed several risk factors (e.g. obesity, inactivity and smoking). The trials mostly included older male patients with CHD, predominantly myocardial infarction (MI). After an initial selection of studies three trials with implausible large effects of RR > 5 which contributed to substantial heterogeneity were excluded. Overall there was a positive effect of interventions on abstinence after six to 12 months (risk ratio (RR) 1.22, 95% CI 1.13,1.32, I^2= 54%; abstinence rate treatment group = 46%, abstinence rate control group 37.4%), but heterogeneity between trials was substantial. Studies with validated assessment of smoking status at follow-up had similar efficacy (RR 1.22, 95% CI 1.07,1.39) to non-validated trials (RR 1.23, 95% CI 1.12,1.35). Studies were stratified by intervention strategy and intensity of the intervention. Clustering reduced heterogeneity, although many trials used more than one type of intervention. The RRs for different strategies were similar (behavioural therapies RR 1.23, 95% CI 1.12,1.34, I^2=40%; telephone support RR 1.21, 95% CI 1.12,1.30, I^2=44%; self-help RR 1.22, 95% CI 1.12,1.33, I^2=40%). More intense interventions (any initial contact plus follow-up over one month) showed increased quit rates (RR 1.28, 95% CI 1.17,1.40, I^2=58%) whereas brief interventions (either one single initial contact lasting less than an hour with no follow-up, one or more contacts in total over an hour with no follow-up or any initial contact plus follow-up of less than one months) did not appear effective (RR 1.01, 95% CI

0.91,1.12, I^2=0%). Seven trials had long-term follow-up (over 12 months), and did not show any benefits. Adverse side effects were not reported in any trial. These findings are based on studies with rather low risk of selection bias but high risk of detection bias. The authors concluded that psychosocial smoking cessation interventions are effective in promoting abstinence up to one year, provided they are of sufficient duration. After one year, the studies showed favourable effects of smoking cessation intervention, but more studies including cost-effectiveness analyses are needed. Further studies should also analyse the additional benefit of a psychosocial intervention strategy to pharmacological therapy (e.g. NRT) compared with pharmacological treatment alone and investigate economic outcomes.[79,Level I]

Stead et al. (2015) assessed the additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. They evaluated the effect of increasing the intensity of behavioural support for people using smoking cessation medications, and to assess whether there are different effects depending on the type of pharmacotherapy, or the amount of support in each condition. Randomized or quasi-randomised controlled trials in which all participants received pharmacotherapy for smoking cessation and conditions differed by the amount of behavioural support were included. The intervention condition had to involve person-to-person contact. The control condition could receive less intensive personal contact, or just written information. They did not include studies that used a contact-matched control to evaluate differences between types or components of support. They excluded trials recruiting only pregnant women, trials recruiting only adolescents, and trials with less than six months follow-up. The main outcome measure was abstinence from smoking after at least six months of follow-up. Forty-seven studies met the inclusion criteria with over 18,000 participants in the relevant arms. There was little evidence of statistical heterogeneity (I^2 = 18%) so pooling of all studies in were conducted. There was evidence of a small but statistically significant benefit from more intensive support (RR 1.17, 95% CI 1.11,1.24) for abstinence at longest follow-up. All but four of the included studies provided four or more sessions of support to the intervention group. Most trials used NRT. The authors did not detect significant effects for studies where the pharmacotherapy was nortriptyline (two trials) or varenicline (one trial), but this reflects the absence of evidence. In subgroup analyses, studies that provided at least four sessions of personal contact for the intervention and no personal contact for the control had slightly larger estimated effects (RR 1.25, 95% CI 1.08 to 1.45; six trials, 3762 participants), although a formal test for subgroup differences was not significant. Studies where all intervention counselling was via telephone (RR 1.28, 95% CI 1.17,1.41; six trials, 5311 participants) also had slightly larger effects, and the test for subgroup differences was significant, but this subgroup analysis was not prespecified. The benefit of providing additional behavioural support was similar for the subgroup of trials in which all participants, including controls, had at least 30 minutes of personal contact (RR 1.18, 95% CI 1.06,1.32; 21 trials, 5166 participants); previously the evidence of benefit in this subgroup had been weaker. This subgroup was not prespecified and a test for subgroup differences was not significant. The authors concluded that providing behavioural support in person or via telephone for people using pharmacotherapy to stop smoking has a small but important effect. Increasing the amount of behavioural support is likely to increase the chance of success by about 10% to 25%, based on a pooled estimate from 47 trials. Subgroup

analysis suggests that the incremental benefit from more support is similar over a range of levels of baseline support.[80,Level I]

Lindson-Hawley Thompson and Begh (2015) conducted a systematic review and meta-analysis to determine whether or not motivational interviewing (MI) promotes smoking cessation. Randomized controlled trials in which motivational interviewing or its variants were offered to tobacco users to assist cessation were selected. The main outcome measure was abstinence from smoking after at least six months follow-up. Twenty-eight studies published between 1997 and 2014, involving over 16,000 participants were included. Motivational interviewing was conducted in one to six sessions, with the duration of each session ranging from 10 to 60 minutes. Interventions were delivered by primary care physicians, hospital clinicians, nurses or counsellors. The meta-analysis of MI versus brief advice or usual care yielded a modest but significant increase in quitting (risk ratio (RR) 1.26, 95% CI 1.16,1.36; 28 studies; N = 16,803). Subgroup analyses found that MI delivered by primary care physicians resulted in an RR of 3.49 (95% CI 1.53 to 7.94; 2 trials; N = 736). When delivered by counsellors the RR was smaller (1.25; 95% CI 1.15 to 1.63; 22 trials; N = 13,593) but MI still resulted in higher quit rates than brief advice or usual care. When they compared MI interventions conducted through shorter sessions (less than 20 minutes per session) to controls this resulted in an RR of 1.69 (95% CI 1.34, 2.12; 9 trials; N = 3651). Single-session treatments might increase the likelihood of quitting over multiple sessions, but both regimens produced positive outcomes. Evidence is unclear on the optimal number of follow-up calls. All trials used some variant of motivational interviewing. Critical details in how it was modified for the particular study population, the training of therapists and the content of the counselling were sometimes lacking from trial reports. The authors concluded that motivational interviewing may assist people to quit smoking. However, the results should be interpreted with caution, due to variations in study quality, treatment fidelity, between-study heterogeneity and the possibility of publication or selective reporting bias.[81,Level I]

Bartlett, Sheeran and Hawley (2014) examined the effectiveness of behavioural change techniques (BCTs) in smoking cessation interventions for people with chronic obstructive pulmonary disease through a meta-analysis. Papers were included if (1) smokers with a diagnosis of COPD were participants, (2) a randomized controlled trial (RCT) of an intervention that aimed to alter participants' behaviour was reported, and (3) a measure of smoking cessation was reported. The outcome measure was smoking cessation (quit rate), measured by either point prevalence (PP) or continuous abstinence (CA) measures. Seventeen RCTs were identified that involved a total sample of 7446 people with COPD. The sample-weighted mean quit rate for all RCTs was 13.19%, and the overall sample-weighted effect size was d+ = 0.33. Thirty-seven BCTs were each used in at least three interventions. Four techniques were associated with significantly larger effect sizes; facilitate action planning or develop treatment plan, prompt self-recording, advice on methods of weight control, and advise on/facilitate use of social support. Three new COPD-specific BCTs were identified, and linking COPD and smoking was found to result in significantly larger effect sizes. The authors concluded that smoking cessation interventions aimed at people with COPD appear to benefit from using techniques focused on forming detailed plans and self-monitoring. Additional RCTs that use standardized reporting of

intervention components and BCTs would be valuable to corroborate findings from the present meta-analysis.[82,Level I]

Bryant et al. (2011) conducted a systematic review and meta-analysis of the effectiveness of behavioural smoking cessation interventions targeted at six disadvantaged groups; the homeless, prisoners, indigenous populations, at-risk youth, individuals with low socio-economic status and individuals with a mental illness. Outcomes examined were abstinence rates at short-term (up to 3 months) and long-term (six months or the longest) follow-up. Thirty-two relevant studies were identified. The majority (*n* = 20) were rated low in methodological quality. Results of the meta-analysis showed a significant increase in cessation for behavioural support interventions targeted at low-income female smokers at short-term follow-up (RR 1.68, CI 1.21,2.33), and behavioural support interventions targeted at individuals with a mental illness at long-term follow-up (RR 1.35, CI 1.01,1.81). Results of the narrative review showed several promising interventions that increased cessation rates at six-month or longer follow-up. Only a few well-controlled trials have examined the most effective smoking cessation strategies for highly disadvantaged groups, especially among the homeless, indigenous smokers and prisoners. The use of behavioural smoking cessation interventions for some socially disadvantaged groups appears promising; however, overall findings are inconsistent. Further research is needed to establish the most effective interventions for vulnerable high-risk groups.[83,Level I]

Bala and Lesniak (2007) evaluated the efficacy of non-pharmacological methods (physician's simple advice and individual and group counseling) used for treating tobacco dependence by conducting a meta-analysis. This study is part of a more comprehensive program analyzing the efficacy and cost-effectiveness of different methods used in smoking cessation. During the first stage of the study, a systematic review of available data was made in order to identify methods used in smoking cessation and assess their efficacy on the basis of already existing reliable systematic reviews or meta-analyses. Seventeen studies included in the most up-to--date and reliable Cochrane systematic review with eight studies assessing efficacy of simple advice provided by a physician. Meta-analyses of RCTs performed during the second part of the study showed that non-pharmacological smoking cessation methods, increased the probability of smoking cessation and smoking abstinence for ≥12 months by 1.5 to 2 times and the number of patients who need to be treated to have one patient who stops smoking was about 30 for more intensive methods and 60 for the physician's simple advice. The study confirmed that non-pharmacological smoking cessation methods available in Poland, i.e. the physician's advice and individual and group counseling, increase the probability of smoking abstinence, and determined the 12-month effects of these interventions.[84,Level I]

b. Technology- Based Methods

Scott-Sheldon et al. (2016) conducted a meta-analysis is to evaluate the efficacy of text messaging interventions on smoking outcomes. Studies were included if they used a randomised controlled trial (RCT) to examine a text messaging intervention focusing on smoking cessation. Twenty studies with 22 interventions (N=15,593; 8128 (54%) women; mean age=29) from 10 countries were included. Smokers who received a text messaging intervention were more likely to abstain from smoking relative to controls across a number

of measures of smoking abstinence including 7-day point prevalence (OR 1.38, 95% CI 1.22, 1.55, k=16) and continuous abstinence (OR 1.63, 95% CI 1.19, 2.24, k=7). Text messaging interventions were also more successful in reducing cigarette consumption relative to controls (d_+=0.14, 95% CI 0.05, 0.23, k=9). The effect size estimates were biased when participants who were lost to follow-up were excluded from the analyses. Cumulative meta-analysis using the 18 studies (k=19) measuring abstinence revealed that the benefits of using text message interventions were established only after only five RCTs (k=5) involving 8,383 smokers (OR 1.39, 95% CI 1.15, 1.67, p<0.001). The inclusion of the subsequent 13 RCTs (k=14) with 6870 smokers did not change the established efficacy of text message interventions for smoking abstinence (OR 1.37, 95% CI 1.25, 1.51, p<0.001). Smoking abstinence rates were stronger when text messaging interventions (1) were conducted in Asia, North America, or Europe, (2) sampled fewer women, and (3) recruited participants via the Internet. The authors concluded that text messaging interventions to reduce smoking are effective. [85, Level 1]

Another study by Whittaker et al. (2016) aimed to update the evidence on the effectiveness of mobile phone-based smoking cessation interventions in people who smoke and want to quit. Randomised or quasi-randomised trials were included. Participants were smokers of any age who wanted to quit. The intervention included any intervention aimed at mobile phone users, based around delivery via mobile phone, and using any functions or applications that can be used or sent via a mobile phone. This updated search identified 12 studies with six-month smoking cessation outcomes, including seven studies completed since the previous review. The interventions were predominantly text messaging-based, although several paired text messaging with in-person visits or initial assessments. Two studies gave pre-paid mobile phones to low-income human immunodeficiency virus (HIV)-positive populations - one solely for phone counselling, the other also included text messaging. One study used text messages to link to video messages. Control programmes varied widely. Studies were pooled according to outcomes - some providing measures of continuous abstinence or repeated measures of point prevalence; others only providing 7-day point prevalence abstinence. All 12 studies pooled using their most rigorous 26-week measures of abstinence provided an RR of 1.67 (95% CI 1.46 to 1.90; I^2 = 59%). Six studies verified quitting biochemically at six months (RR 1.83; 95% CI 1.54 to 2.19). The authors concluded that the current evidence supports a beneficial impact of mobile phone-based smoking cessation interventions on six-month cessation outcomes. While all studies were good quality, the fact that those studies with biochemical verification of quitting status demonstrated an even higher chance of quitting further supports the positive findings. However, it should be noted that most included studies were of text message interventions in high-income countries with good tobacco control policies.[86,Level I]

Stanczyk et al. (2016) examined the effectiveness of video- versus text-based computer-tailored smoking cessation interventions among smokers after one year. A randomised controlled trial in the Netherlands was used in which smokers were allocated to the video-based condition (VC) (N = 670), the text-based condition (TC) (N = 708) or the control condition (CC) (brief generic text advice) (N=721). After 12 months, self-reported prolonged abstinence was assessed and biochemically verified in respondents indicating to have quit smoking. Three analysis strategies were used to assess the effects: (1) multiple imputation (MI); (2) intention-to-treat (ITT); (3) complete case

analysis (CC). Video-based condition was more effective in prolonged abstinence compared to control (odds ratio (OR) = 1.90, p =0.005) and the text-based condition (OR = 1.71, p = .01). No differences were found for SES and motivational levels. Results were similar when using ITT and CC. In terms of seven-day point prevalence abstinence; however, neither VC (OR = 1.17, p = 0.34) or TC (OR = 0.91, p = 0.52) outperformed the CC. The authors concluded that the video-based computer-tailored intervention was effective in obtaining substantial long-term abstinence compared to the text-based version and a brief generic text advice. [87,Level 1]

Bottorff et al. (2016) evaluated QuitNow Men, an online, men-centered smoking cessation intervention programme based on focus group interview findings, stakeholder feedback, and evidence-based cessation strategies. The website was designed to incorporate a masculine look and feel through the use of images, direct language, and interactive content. Usability experts and end-users provided feedback on navigation and functionality of the website prior to pilot testing. The objectives of the study were to describe (1) men's use and evaluations of the interactive resources and information on the QuitNow Men website, and (2) the potential of QuitNow Men to engage men in reducing and quitting smoking. A pretest-posttest study design was used. Men who were interested in quitting were recruited and invited to use the website over a six-month period. Data were collected via online questionnaires at baseline, 3-month, and six-month follow-up. A total of 117 men completed the baseline survey. Over half of those (67/117, 57.3%) completed both follow-up surveys. At baseline, participants (N=117) had been smoking for an average of 24 years (SD 12.1) and smoked on average 15 cigarettes a day (SD 7.4). The majority had not previously used a quit smoking website (103/117, 88.0%) or websites focused on men's health (105/117, 89.7%). At the six-month follow-up, the majority of men used the QuitNow Men website at least once (64/67, 96%). Among the 64 users, 29 (43%) reported using the website more than six times. The men using QuitNow Men agreed or strongly agreed that the website was easy to use (51/64, 80%), the design and images were appealing (42/64, 66%), they intended to continue to use the website (42/64, 66%), and that they would recommend QuitNow Men to others who wanted to quit (46/64, 72%). Participants reported using an average of 8.76 (SD 4.08) of the 15 resources available on the website. At six-month follow-up, 16 of the 67 participants (24%) had quit, 27 (40%) had reduced their smoking and 24 (36%) had not changed their smoking habits. Repeated measures general linear model showed a significant decrease in the number of cigarettes smoked between the 3-month and six-month follow-up ($F_{1,63}$=6.41, p=0.01, eta squared=0.09). Number of resources used on the website, quit confidence, nicotine dependence and age significantly predicted number of quit attempts by those still smoking at six months ($F_{4,45}$=2.73, p=0.04), with number of resources used being the strongest predictor (p=0.02). The results of this research support efforts to integrate gender-sensitive approaches in smoking cessation interventions and indicate that this novel web-based resource has potential in supporting men's smoking cessation efforts.[88,Level II-I]

Another meta-analysis was conducted by Spohr et al. (2015) to evaluate SMS (short message service) text message-based interventions for individual smoking cessation. The included studies were those which are 1) randomised controlled trials, 2) measured smoking cessation, and 3) intervention primarily delivered through SMS text messaging. Three and six-month follow-up of 7-

day point prevalence or continuous abstinence was considered from studies meeting criteria. All analyses were conducted with intention-to-treat. Both fixed and random effects models were used to calculate the global outcome measure and confidence intervals. Thirteen studies were identified that met inclusion criteria. The studies were found to be homogeneous [Q_{12}=10.89, p=0.54]. Odds ratios suggested that interventions generally increased quit rates compared to controls, 1.35 (95% CI 1.23, 1.48). Intervention efficacy was higher in studies with a 3-month follow-up compared to six month follow-up. Text plus programmes (e.g., text-messaging plus Web or in-person intervention modalities) performed only slightly better than text only programmes. Pooled results also indicate message frequency schedule can affect quit rates, in which fixed schedules performed better than decreasing or variable schedules. The use of quit status assessment messages was not related to intervention efficacy. Smoking quit rates for the text messaging intervention group were 35% higher compared to the control group quit rates. The author concluded that SMS text messaging may be a promising way to improve smoking cessation outcomes. This is significant given the relatively wide reach and low cost of text message interventions.[89,Level I]

Cheung et al. (2015) examined the usage of WhatsApp and Facebook online social groups and their effectiveness for smoking relapse prevention for recent quitters. A single-blinded, parallel, three arm pilot cluster randomised controlled trial allocating recent quitters, who had completed an eight weeks treatment and reported abstinence for at least seven days, to WhatsApp (n=42), Facebook (n=40), and a control group (n=54). The two intervention groups participated in a two months online group discussion with either WhatsApp or Facebook moderated by a trained smoking cessation counsellor and received a self-help booklet on smoking cessation. The control group only received the booklet. The primary outcome was the two and six months relapse rates, defined as the proportion of participants who smoked at least five cigarettes in three consecutive days. The study found that fewer participants in the WhatsApp group (17%, 7/42) reported relapse than the control group (42.6%, 23/54) at 2 months (OR 0.27, 95% CI 0.10,0.71) and six months (40.5%, 17/42 versus 61.1%, 33/54; OR 0.43, 95% CI 0.19,0.99) follow-ups. The Facebook group (30.0%, 12/40) had an insignificantly lower relapse rate than the control group (42.6%, 23/54) at 2 month (OR 0.58, 95% CI 0.24,1.37) and six months (52.5%, 13/40 versus 61.1%, 33/54; OR 0.70, 95% CI 0.31,1.61) follow-ups. The WhatsApp social groups had more moderators' posts (median 60, IQR 25 versus median 32, IQR 7; *p*=0.05) and participants' posts (median 35, IQR 50 versus median 6, IQR 9; *p*=0.07) than their Facebook counterparts, but the difference was insignificant. The authors concluded that the intervention via the WhatsApp social group was effective in reducing relapse probably because of enhanced discussion and social support. Inactive discussion in the Facebook social group might have attributed to the lower effectiveness.[90,level II-I]

Park and Drake (2015) conducted a systematic review to determine the characteristics and effects internet-based youth smoking prevention and cessation programs. Published articles in peer-reviewed journals in the past 10 years which focused on internet-based youth smoking prevention and cessation programs were included. Twelve articles were selected based on the following criteria: studies reporting the outcomes of internet-based smoking cessation or prevention intervention programs for adolescents who are younger than 24 years. In total, 10,016 participants were included in the

12 studies, with ages varied from 11 to 23 years. The majority of studies focused on either middle school students, high school students or both. Most studies assessed smoking behaviour (point 30-day abstinence, point 7-day abstinence) as a primary outcome, and four studies confirmed self-report with biochemical measures in smoking cessation studies. Smoking uptake, intention, attitudes, self-efficacy, and knowledge are common constructs used to evaluate the effect of smoking prevention. Follow-up assessments were conducted anywhere from immediately post-intervention to six months later with various outcome measures, depending on the purpose of the studies. The components of youth internet-based smoking intervention programs were analysed based on study features (i.e., sample, design, theoretical basis, analysis, outcome measures) and program characteristics (i.e., focus, setting, frequency, duration, intensity, and different components) that make the programs effective. The most common components of effective internet-based programs are identified as the following: the use of multimedia, tailored approaches, personalized feedback, and interactive features. The characteristics and effects of the programs vary, but most studies showed positive outcomes in the efficacy of internet-based components, with higher rates of quitting smoking in the intervention group compared to the control group with statistical significance, including immediately post-intervention and at 3 months. Only one study reported the opposite results in which, the treatment group without personal components tended to report lower quit rates compared to the control group. Quit rates varied ranging from 4.9% to 16.2% at post-intervention. Higher quit rates in treatment groups than control groups did not show statistical significance at three months, six months, 12 months and 14 months. In most studies, significant positive results were not reported with long-term follow-up. For smoking prevention programs, youth in the treatment group showed positive results in decreasing their intention to smoke with statistical significance in most studies. [91,Level I]

c. Quitlines

Use and effectiveness of quitlines versus web-based tobacco cessation interventions among four states tobacco control programs were evaluated by Neri et al. (2016) in a comparative study. Standardized questionnaires were administered to smokers who enrolled exclusively in either quitlines or Web-based tobacco cessation services in 4 states in 2011-2012. The primary outcome was the 30-day point prevalence abstinence (PPA) rate at 7 months both between and within interventions. A total of 4,086 participants were included in the analysis. Quitline users were significantly older, more heterogeneous in terms of race and ethnicity, less educated, less likely to be employed, and more often single than web-based users. The 7-month 30-day PPA rate was 32% for quitline users and 27% for Web-based users. Multivariate models comparing 30-day PPA rates between interventions indicated that significantly increased odds of quitting were associated with being partnered, not living with another smoker, low baseline cigarette use, and more interactions with the intervention. After adjustments for demographic and tobacco use characteristics, quitline users had 1.26 the odds of being abstinent in comparison with web-based users (95% CI 1.00,1.58; p=0.053). The authors concluded that there was no significant difference in 30-day PPA at 7 month follow-up for web-based users versus quitline users in multivariate models. These results indicate the need for more in-depth analyses including cost-analysis related to what components of web-based interventions work in specific populations to help public health

agencies develop and tailor evidence-based tobacco cessation programs.[92,Level II-3]

Meeyai et al. (2015) evaluated the usage patterns, effectiveness and cost of the national smoking cessation quitline in Thailand (TNQ). Analysis of retrospective data for callers to the TNQ between 2009 and 2012 and a follow-up survey in 1161 randomly selected callers. Between 2009 and 2012 there were 116,862 callers to the TNQ; 36 927 received counselling and at least one follow-up call. Compared with smokers in the general population, callers were younger, more highly educated, more likely to be students, and more likely to smoke cigarettes rather than roll-your-own tobacco. Continuous abstinence rates at one, three and six months after calling were 49.9%, 38.0% and 33.1%. The predicted rate at 12 months was 19.54% (95% CI 14.55, 26.24). Average cost per completed counselling was USD 31 and the average cost per quitter was USD 253. The overall cumulative life years saved (LYS) due to the TNQ for the 4-year period was estimated to be 57,238 and the cost per LYS was estimated to be USD 31.83, assuming no quitters would have quit without TNQ.
If one-fifth of quitters would have quit anyway (without TNQ support), the cumulative LYS due to the TNQ for the 4-year period would be 45,521 (with a cost per LYS of USD 40.02). Corresponding numbers with a quit rate without assistance of one-third would be 36 773 (with a cost per LYS of USD 49.59). An estimated return on investment over 4 years were 9.01 (5.78). The authors concluded that a low-cost quitline without NRT is a promising model for smoking cessation services and likely to offer good value for money in Thailand.[93, Level II-2]

McDaniel et al. (2015) conducted a randomised controlled trial to prevent smoking relapse among recently quit smokers enrolled in employer and health plan sponsored quitlines - Quit for Life (QFL) programme. Their aim was to test whether adding an interactive voice response (IVR)-supported protocol to standard quitline treatment prevent relapse among recently quit smokers. The study design was parallel randomised controlled trial with three arms: standard quitline, standard plus technology enhanced quitline with ten risk assessments (TEQ-10), standard plus 20 TEQ assessments (TEQ-20). Participants were 1785 QFL enrollees through 19 employers or health plans who quitted for more than 24 hours. Quit for Life programme is a 5-call telephone-based cessation programme including medications and web based support. Technology enhanced quitline interventions included ten or 20 IVR-delivered relapse risk assessments over 8 weeks with automated transfer to counselling for those at risk. The main outcome measures were self-reported 7-day and 30-day abstinence assessed at six-month and 12-month post-enrolment (response rates: 61% and 59%, respectively). The participants were randomised to standard therapy n=592, TEQ-10 n=602 and TEQ-20 n=591. Multiple imputation derived, intent-to-treat 30-day quit rates (95% CI) at six months were 59.4% (53.7% to 63.8%) for standard, 62.3% (57.7% to 66.9%) for TEQ-10, 59.4% (53.7% to 65.1%) for TEQ-20 and 30-day quit rates at12 months were 61.2% (55.6% to 66.8%) for standard, 60.6% (56.0% to 65.2%) for TEQ-10, 54.9%(49.0% to 60.9%) for TEQ-20. There were no significant differences in quit rates. Seventy three percent of TEQ participants were identified as at-risk by IVR assessments; on average, participants completed 0.41 IVR-transferred counselling calls. Positive risk assessments identified participants less likely (OR 0.56, 95% CI 0.42, 0.76) to be abstinent at six months. The authors concluded that standard treatment was highly

effective, with 61% remaining abstinent at 12 months using multiple imputation intent-to-treat (intent-to-treat missing=smoking quit rate: 38%). TEQ assessments identified quitters at risk for relapse. However, adding IVR-transferred counselling did not yield higher quit rates. [94, Level I]

Lukowski et al. (2015) evaluated the quitline outcomes for smokers in six states varied by their mental health status. Up to half of quitline callers report a history of mental health conditions and/or recent emotional challenges (MH+), and there has been little study of cessation outcomes for this population. Moreover, evidence suggests that callers who expect their MH+ to interfere with quit attempts have less success with quitting. This study compared rates of quitting among MH+callers and callers with no mental health conditions or recent emotional challenges (MH−). It also compared rates of quitting between those who felt that mental health issues would interfere with their quit attempt (MHIQ+) and those who did not (MHIQ−). The study utilised National Jewish Health telephone data from six state quitlines. Participants received up to five coaching sessions and up to eight weeks of NRT. Smoking status was assessed during 3-month and six-month post-intervention calls in a subset of participants (n = 4,960) for whom follow-up interviews were completed. Participation in follow-up interviews was not significantly different between callers with MH+ and those without MH− (p =0.13). However, at follow-up MH+ participants were less likely to report a successful quit compared with MH− (three-month: 31% versus. 43%; six-month: 33% versus. 43%; both $p < 0.001$). Among MH+ participants, those reporting MHIQ+ were significantly less likely to quit compared with those who were MHIQ− (3-month: 24% versus. 34%; six-month: 26% versus. 35%; both $p \leq 0.001$). These findings highlight the importance of evaluating both the mental health status of individuals seeking support for smoking cessation as well as the individuals' expectations for success, because they may need more tailored intervention to ensure the potential for better compared with outcomes. [95, Level II-2]

Blebil et al. (2014) examined the impact of additional counselling sessions through phone calls on smoking cessation outcomes among smokers in Penang State, Malaysia. They aimed to assess the impact of the additional phone calls counselling during the first month on the abstinence rate at three and six months after quit date among smokers at quit smoking clinic of two major hospitals in Penang, Malaysia. Participants were randomly assigned either to receive the usual care that followed in the clinics (control) or the usual care procedure plus extra counselling sessions through phone calls during the first month of quit attempt (intervention). Overall, participants smoked about 14 cigarettes per day on average (mean = 13.78, SD 7.0). At three months, control group was less likely to quit smoking compared to intervention group (36.9% versus. 46.7%, verified smoking status) but this did not reach statistical significance (OR 0.67, 95% CI 0.39,1.13, p = 0.86). However, at six months, 71.7% of the intervention group successfully quit smoking (bio-chemically verified) compared to 48.6% of the control group (p < 0.001). The control group were significantly less likely to quit smoking (OR 0.38, 95% CI 0.22,0.65, p< 0.001). The authors concluded that smoking cessation intervention consisting of phone calls counselling delivered during the first month of quit attempt revealed significantly higher abstinence rates compared with a standard care approach. Therefore, the additional counselling in the first few weeks after stop smoking is a promising treatment strategy that should be evaluated further. [96, Level I]

Lavender et al. (2013) evaluated the telephone support for women during pregnancy and the first six weeks postpartum. Their aim was to assess the effects of telephone support during pregnancy and the first six weeks post birth, compared with routine care, on maternal and infant outcomes. Randomised controlled trials, comparing telephone support with routine care or with another supportive intervention aimed at pregnant women and women in the first six weeks post birth were included. Data from 27 randomised trials involving 12,256 women were finally included. All of the trials examined telephone support versus usual care (no additional telephone support). The author did not identify any trials comparing different modes of telephone support (for example, text messaging versus one-to-one calls). All but one of the trials was carried out in high-resource settings. The majority of studies examined support provided via telephone conversations between women and health professionals although a small number of trials included telephone support from peers. In two trials women received automated text messages. Many of the interventions aimed to address specific health problems and collected data on behavioural outcomes such as smoking cessation and relapse (seven trials) or breastfeeding continuation (seven trials). Other studies examined support interventions aimed at women at high risk of postnatal depression (two trials) or preterm birth (two trials); the rest of the interventions were designed to offer women more general support and advice. Overall, results were inconsistent and inconclusive although there was some evidence that telephone support may be a promising intervention. Results suggest that telephone support may increase women's overall satisfaction with their care during pregnancy and the postnatal period, although results for both periods were derived from only two studies. There was no consistent evidence confirming that telephone support reduces maternal anxiety during pregnancy or after the birth of the baby, although results on anxiety outcomes were not easy to interpret as data were collected at different time points using a variety of measurement tools. There was evidence from two trials that women at high risk of depression who received support had lower mean depression scores in the postnatal period, although there was no clear evidence that women who received support were less likely to have a diagnosis of depression. Results from trials offering breastfeeding telephone support were also inconsistent, although the evidence suggests that telephone support may increase the duration of breastfeeding. There was no strong evidence that women receiving telephone support were less likely to be smoking at the end of pregnancy or during the postnatal period. For infant outcomes, such as preterm birth and infant birthweight, overall, there was little evidence. Where evidence was available, there were no clear differences between groups. Results from two trials suggest that babies whose mothers received support may have been less likely to have been admitted to a neonatal intensive care unit (NICU), although it is not easy to understand the mechanisms underpinning this finding. The authors concluded that despite some encouraging findings, there is insufficient evidence to recommend routine telephone support for women accessing maternity services, as the evidence from included trials is neither strong nor consistent. Although benefits were found in terms of reduced depression scores, breastfeeding duration and increased overall satisfaction, the current trials do not provide strong enough evidence to warrant investment in resources.[97, Level I]

Stead et al. (2007) conducted a systematic review to evaluate the effect of different types of adjunctive support to stop smoking for individuals contacting

telephone quitlines, including call-back counselling, different counselling techniques and provision of self-help materials. The review includes quitline studies identified as part of Cochrane reviews of telephone counselling and self-help materials for smoking cessation. The included studies were randomised or quasi-randomised controlled trials of any quitline or related service with follow-up of at least six months. The cessation outcome was numbers quit at longest follow-up taking the strictest definition of abstinence available, and assuming participants lost to follow-up continued to smoke. A total of 14 relevant studies identified. Eight studies (18,500 participants) comparing multiple call-backs to a single contact increased quitting in the intervention group (Mantel-Haenszel fixed effect odds ratio 1.41, 95% CI 1.27,1.57). Two unpublished studies without sufficient data to include in the meta-analysis also reported positive effects. Three call-back trials compared two schedules of multiple calls. Two found a significant dose-response effect and one did not detect a difference. The authors did not find consistent differences in comparisons between counselling approaches (two trials) or between different types of self-help materials supplied following quitline contact (three trials). Multiple call-back counselling was found to improve long term cessation for smokers who contact quitline services. Offering more calls may improve success rates. However, the study failed to detect an effect of the type of counselling or the type of self-help materials supplied as adjuncts to quitline counselling.[98, Level I]

Tinkelman et al. (2007) evaluated whether offering free NRT through a tobacco quitline has an impact on utilisation and quit rates. Tobacco use status data from the Ohio tobacco quitline were collected from a subset of quitline callers six months after the initial intake call. Quit rates for two groups were compared: those who entered and exited the quitline programme before the availability of free NRT (n = 4657) and those who entered and exited the quitline programme after the availability of free NRT (n = 5715). The study found that call volume increased from 2351 intakes calls per month or 78 calls per day before the availability of free NRT to 3606 intake calls per month or 188 intakes per day following the availability of free NRT(p=0.0001). Seven-day point prevalence abstinence at six months among all quitline callers increased from 10.3% (95% CI 9.7, 10.9) before the availability of NRT to 14.9% (95% CI 14.3,15.5) after the availability of NRT. The authors concluded that offering free NRT through a state quitline is an effective means of increasing quitline utilization and improving quit rate.[99,Level II-3]

Maher et al. (2007) assessed whether smoking quit rates and satisfaction with the Washington State tobacco quitline (QL) services varied by race/ethnicity, socioeconomic status, area of residence (urban versus non-urban), or sex of Washington QL callers. From October 2004 into October 2005, they conducted telephone surveys of Washington QL callers about three months after their initial call to the QL. Analyses compared seven-day quit rates and satisfaction measures by race/ethnicity, education level, area of residence and sex (using a = 0.05). The authors surveyed half (n = 1312) of the 2638 adult smokers that they attempted to contact. The 7-day quit rate among survey participants at the 3-month follow-up was 31% (95% CI 27.1%, 34.2%), 92% (95% CI 89.9%, 94.1%) were somewhat/very satisfied overall with the QL programme, 97% (95% CI 95.5%,98.2%) indicated that they would probably/for sure suggest the QL to others and 95% (95% CI 92.9%,96.4%) were somewhat/very satisfied with the QL specialist. Quit rate did not vary significantly by race/ethnicity, education level, area of residence

or sex. Satisfaction levels were high across subpopulations. Almost all participants (99%) agreed that they were always treated respectfully during interactions with QL staff. Overall, the Washington QL appeared effective and well received by callers from the specific populations studied. States choosing to promote their QL more aggressively should feel confident that a tobacco QL can be an effective and well received cessation service for smokers who call from a broad range of communities.[100, level II-3]

Pan (2006) conducted a meta-analysis evaluating proactive telephone counselling as an adjunct to minimal intervention for smoking cessation. They reviewed 22 studies published between January 1990 and December 2003 and found that there was a heterogeneous, significant adjunct effect of proactive telephone counseling for smoking cessation. The study also found that the following study characteristics explained most of the variation in the adjunct effect: year of publication, follow-up time, mean age of participants, proportion of female participants, participants' readiness to quit smoking and number of cigarettes smoked per day before intervention. In other words, based on the 22 studies, proactive telephone counseling is effective as an adjunct to other minimal interventions for younger, male, light-smoking participants. The results of this meta-analytic review imply that researchers and health care providers may need to focus on participants as much as on intervention process to obtain more effective interventions.[101,level I]

Solomon et al. (2005) examined whether extended proactive telephone support increase smoking cessation among low-income women using nicotine patches. The authors recruited participants throughout Vermont by posting flyers about the study in health care and human service agencies and on public bulletin boards. The flyers offered free nicotine patches to women smokers who met the study guidelines. Interested smokers called a toll-free number to be screened for eligibility. They randomly assigned 330 low-income women smokers to receive either free nicotine patches (control condition) or free nicotine patches with up to 16 weeks of proactive telephone support (experimental condition). All participants were assessed by telephone at baseline and at two weeks, three months, and six months post-baseline to determine smoking status. Results revealed a significant effect for the telephone support at three months, with 43% of experimental versus 26% of control condition women reporting 30-day point prevalent abstinence ($p = 0.002$). The difference was no longer significant at six months. A meta-analysis was conducted with five randomised studies revealed a slight but non-significant long-term benefit of proactive telephone support when added to the provision of free nicotine patches for smoking cessation. There was short-term effect for proactive telephone support added to free NRT; however, neither the current study, nor the meta-analysis including the four other published trials, confirmed a longer term benefit.[102,Level I]

d. Incentives

Parks et al. (2016) evaluated interpersonal communication (IPC) in response to incentive-based, population-level programmes and perceived importance of the incentive for the incentivized behavior (i.e., being connected to a quitline) relate to both short-term and long-term health behaviour change.This study used survey data gathered after a population-level telehealth intervention that offered $20 incentives to low-income smokers for being connected to free quitline (QL) under Minnesota's National Breast and Cervical Cancer Early

Detection Programme (Sage). Sage provides free cancer screening services to individuals who are ages 40 years or older, have household incomes at or below 250% of the federal poverty level,and are inadequately insured. Interpersonal communication about the incentive-based programme was measured as whether participants ‘‘told others about the Sage offer that rewards smokers $20 for being connected with a tobacco quitline through the Sage Call Center’’. Of the surveyed participants who were offered QL services, 643 individuals (66%) were connected to the QL and utilized the services, such as receiving telephone counselling or self-help materials. In terms of 30-day point prevalence quit rates, 19% reported continuous cessation 7 months after QL connection (184 individuals) while 50% engaged in IPC about the incentive-based program, and almost 69% noted that the incentive was important for their QL connection. Interpersonal communication was strongly associated with initial quitline utilization and continuous smoking abstinence as measured by 30-day point prevalence rates at 7-month follow-up. Perceived incentive importance had weak associations with both measures of cessation, and all associations were nonsignificant in models adjusting for IPC. The authors concluded that a behavioural telehealth intervention targeting low-income smokers that offered a financial incentive inspired IPC, and this social response was strongly related to utilization of intervention services as well as continuous smoking abstinence.[103, Level II-3]

Cahill et al. (2015) determined whether incentives and contingency management programmes lead to higher long-term quit rates in a systematic review and meta-analysis. Randomised controlled trials, allocating individuals, workplaces, groups within workplaces, or communities to experimental or control conditions were considered. They included studies in a mixed-population setting (e.g. community-, work-, institution-based), and also, for this update, trials in pregnant smokers. The main outcome measure in the mixed-population studies was abstinence from smoking at longest follow-up, and at least six months from the start of the intervention. In the trials of pregnant smokers abstinence was measured at the longest follow-up, and at least to the end of the pregnancy. Twenty-one mixed-population studies met the inclusion criteria, covering more than 8400 participants. Ten studies were set in clinics or health centres, one in Thai villages served by community health workers, two in academic institutions, and the rest in worksites. All but six of the trials were run in the USA. The incentives included lottery tickets or prize draws, cash payments, vouchers for goods and groceries, and in six trials the recovery of money deposited by those taking part. The OR for quitting with incentives at longest follow-up (six months or more) compared with controls was 1.42 (95% CI 1.19,1.69; 17 trials, [20 comparisons], 7715 participants). Only three studies demonstrated significantly higher quit rates for the incentives group than for the control group at or beyond the six-month assessment: One five-arm USA trial compared rewards- and deposit-based interventions at individual and group level, with incentives available up to USD 800 per quitter, and demonstrated a quit rate in the rewards groups of 8.1% at 12 months, compared with 4.7% in the deposits groups. A direct comparison between the rewards-based and the deposit-based groups found a benefit for the rewards arms, with an OR at 12 months of 1.76 (95% CI 1.22 to 2.53; 2070 participants). Although more people in this trial accepted the rewards programmes than the deposit programmes, the proportion of quitters in each group favoured the deposit-refund programme. Another USA study rewarded both participation and quitting up to USD 750, and achieved sustained quit rates of 9.4% in the incentives group compared with 3.6% for

the controls. A deposit-refund trial in Thailand also achieved significantly higher quit rates in the intervention group (44.2%) compared with the control group (18.8%), but uptake was relatively low, at 10.5%. In the remaining trials, there was no clear evidence that participants who committed their own money to the programme did better than those who did not, or that contingent rewards enhanced success rates over fixed payment schedules. The overall quality of the older studies was rated as low, but with later trials (post-2000) more likely to meet current standards of methodology and reporting. In conclusion, incentives appear to boost cessation rates while they are in place. The two trials recruiting from work sites that achieved sustained success rates beyond the reward schedule concentrated their resources into substantial cash payments for abstinence. Such an approach may only be feasible where independently-funded smoking cessation programmes are already available, and within a relatively affluent and educated population. Deposit-refund trials can suffer from relatively low rates of uptake, but those who do sign up and contribute their own money may achieve higher quit rates than reward-only participants. Incentive schemes conducted among pregnant smokers improved the cessation rates, both at the end-of-pregnancy and post-partum assessments. [104,Level I]

Yeo et al. (2015) evaluated the efficacy of the financial incentives given to various teams in the workplace. St. Paul's Hospital's employees were enrolled in this study. Each team of employees consisted of smoking participants and non-smoking fellow workers from the same department. The financial incentive of 50,000 won (about USD45) was rewarded to the team for each successful participant-not to individual members-after the first week and then after one month. If the smokers in the team remained abstinent for a longer time period, the team was given an incentive of 100,000 won for each successful participant after three and six months. A total 28 smoking participants and six teams were enrolled. Self-reported abstinence rates validated by urinary cotinine test at three, six, and 12 months after the initial cessation were 61%, 54%, and 50%, respectively. Smokers with high nicotine dependence scores or those who began participation one month after enrolment initiation had a lower abstinence rate at three months, but not at six and 12 months. Participants who succeeded at smoking cessation at 12 months were more likely to be older and have a longer smoking duration history. The financial incentives given to teams could be promising and effective to improve long-term rates of smoking cessation. This approach could use peer pressure and peer support in the workplace over a longer period.[105, Level III]

O'Connor et al. (2006) evaluated a tobacco control programme across the New York state which held 'Quit and Win' incentive-based stop-smoking contests. These contests encouraged smokers to make a quit attempt by offering a chance to win cash prize (around USD1,000) for successfully stopping smoking for at least one month. Between 2001 and 2004, 11 different Quit and Win Contests involving 5,504 adult smokers were sponsored in different communities across New York State. Follow-up surveys were conducted four to six months after each contest ended to evaluate participants' success in quitting smoking. Quit rate is based on the self-reported smoking status at the time of the follow-up telephone interview. Participants who reported not smoking currently and also reported no cigarettes smoked in the 7 days prior to the interview were defined as having quit. Expenditures for promoting contests varied from a high of USD 91,441 to

a low of USD 4,345, with a median of USD 25,928. An average of 0.55% of smokers was recruited to join contests across the 11 communities. Among smokers who enrolled in a contest, 9 out of 10 reported making a quit attempt, and between 53% and 72% reported quitting for the full month of the contest. At four to six months follow-up, self-reported quit rates (7-day point prevalence) among contestants ranged from 22% to 49%, with an average of 31%. Based on a state-wide population survey, eight of the 11 programs showed quit rates that were significantly higher ($p < 0.001$) than the estimated quit rate of 21% seen among smokers making a quit attempt in the past year. This study showed that for a relatively modest investment of resources, thousands of smokers can be recruited to make a serious quit attempt, with many remaining smoke-free months later.[106,Level II-3]

e. Self-Help Materials

Blyth et al. (2015) conducted health technology assessment to evaluate the effectiveness of self-help educational materials for the prevention of smoking relapse in people who had stopped smoking with the aid of behavioural support. It was an open, randomised controlled trial and qualitative process evaluation. Trial participants were randomly allocated to one of two groups, using a simple randomisation process. The participant allocation was 'concealed' because the recruitment of quitters occurred before the random allocation. Short-term quitters were recruited from NHS Stop Smoking Clinics, and self-help educational materials were posted to study participants at home. A total of 1407 CO-validated quitters at four weeks after quit date in NHS Stop Smoking Clinics participated in the study. The trial excluded pregnant women and quitters who were not able to read the educational materials in English. Participants in the experimental group (n = 703) received a set of eight revised Forever Free booklets, and participants in the control group (n = 704) received a single leaflet that is currently given to NHS patients. The main outcome measures include follow-up telephone interviews conducted three and 12 months after quit date. The primary outcome was prolonged, CO-verified abstinence from month's 4 to 12 during which time no more than five cigarettes were smoked. The secondary outcomes included self-reported abstinence during the previous seven days at three and 12 months, CO-verified abstinence at 12 months, costs (NHS and participant medication costs perspectives) and quality-adjusted life-years. A simultaneous qualitative process evaluation was conducted to help interpret the trial results. Data from 1404 participants were used for the final analysis. The proportion with prolonged abstinence from months four to 12 after quit date was 36.9% in the intervention group and 38.6% in the control group. There was no statistically significant difference between the groups (OR 0.93, 95% CI 0.75,1.15; p = 0.509). There were no statistically significant differences between the groups in secondary smoking outcomes. People who reported knowing risky situations for relapse and using strategies to handle urges to smoke were less likely to relapse. However, there were no differences between the groups in the proportion of participants who reported that they knew any more about coping skills, and no differences in reported use of strategies to cope with urges to smoke between the trial groups. The qualitative study found that some quitters considered self-help booklets unhelpful for smoking relapse prevention, although positive feedback by participants was common. Among quitters who had stopped smoking with the aid of intensive behavioural support, there was no significant difference in the likelihood of smoking relapse between those who subsequently received a set

of eight revised Forever Free booklets and those who received a single leaflet. [107,Level 1]

6.1.4. EFFECTIVENESS OF COMPLEMENTARY AND ALTERNATIVE INTERVENTIONS

Five articles (studies) related to the effectiveness of complementary and alternative interventions for quit smoking met the inclusion criteria and included in this review.

a. Hypnotherapy

Hasan et al. (2014) compared the efficacy of hypnotherapy alone, as well as hypnotherapy with NRT, to conventional NRT in patients hospitalized with a cardiac or pulmonary illness. They evaluated self-reported and biochemically verified 7-day prevalence smoking abstinence rates at 12 and 26 weeks post-hospitalization. Patients (n=164) were randomised into one of three counselling-based treatment groups: NRT for 30 days (n=41), a 90-minutes hypnotherapy session (n=39), and NRT with hypnotherapy (n=37). Treatment groups were compared to a "self-quit" group of 35 patients who refused intervention. The study found that hypnotherapy patients were more likely than NRT patients to be non-smokers at 12 weeks (43.9% versus. 28.2%; p=0.14) and 26 weeks after hospitalization (36.6% vs. 18.0%; p=0.06). Smoking abstinence rates in the NRT with hypnotherapy group were similar to the hypnotherapy group. There was no difference in smoking abstinence rates at 26 weeks between "self-quit" and participants in any of the treatment groups. In multivariable regression analysis adjusting for diagnosis and demographic characteristics, hypnotherapy and NRT with hypnotherapy were over three times more likely than NRT participants to abstain at 26-weeks post-discharge (RR=3.6; p=0.03 and RR=3.2; p=0.04, respectively). The authors concluded that hypnotherapy is more effective than NRT in improving smoking abstinence in patients hospitalized for a smoking-related illness. However, these results should be interpreted with caution due to the small sample sizes. [108,Level II-I]

Tahiri, Mottillo and Joseph (2012) conducted a meta-analysis of randomised controlled trials to determine the efficacy of alternative smoking cessation aids. They included trials that reported cessation outcomes as point prevalence or continuous abstinence at six or 12 months. Fourteen trials were identified; six investigated acupuncture (823 patients); four investigated hypnotherapy (273 patients); and four investigated aversive smoking (99 patients). The estimated mean treatment effects were acupuncture (OR 3.53, 95% CI 1.03,12.07), hypnotherapy (OR 4.55 95% CI 0.98,21.01), and aversive smoking (OR 4.26, 95% CI 1.26,14.38). The authors found that acupuncture and hypnotherapy may help smokers quit. Aversive smoking also may help smokers quit; however, there are no recent trials investigating this intervention. More evidence is needed to determine whether alternative interventions are as efficacious as pharmacotherapies. [109, Level 1]

In an earlier meta-analysis by Barnes et al. (2010) who evaluated the efficacy of hypnotherapy for smoking cessation, they found 11 studies which compared hypnotherapy with 18 different control interventions. There was significant heterogeneity between the results of the individual studies, with conflicting results for the effectiveness of hypnotherapy compared to no

treatment, or to advice, or psychological treatment. There was no evidence of a greater effect of hypnotherapy when compared to rapid smoking or psychological treatment. Direct comparisons of hypnotherapy with cessation treatments considered to be effective had confidence intervals that were too wide to infer equivalence. The authors concluded that hypnotherapy has a greater effect on six-month quit rates than other interventions or no treatment. However, there is not enough evidence to show whether hypnotherapy could be as effective as counselling treatment. The effects of hypnotherapy on smoking cessation claimed by uncontrolled studies were not confirmed by analysis of randomised controlled trials.[110,Level I]

b. Acupuncture

In a systematic review with meta-analysis, White et al. (2014) evaluated the effectiveness of acupuncture and the related interventions of acupressure, laser therapy and electrostimulation in smoking cessation, in comparison with no intervention, sham treatment, or other interventions. Randomized trials on these interventions with outcomes measuring abstinence from smoking at the earliest time-point (before six weeks) and at the last measurement point between six months and one year were selected. Thirty eight studies were finally included. Based on three studies, acupuncture was not shown to be more effective than a waiting list control for long- term abstinence, with wide CI and evidence of heterogeneity (n = 393, RR 1.79, 95% CI 0.98,3.28, I^2 = 57%). Compared with sham acupuncture, the RR for the short-term effect of acupuncture was 1.22 (95% CI 1.08,1.38), and for the long-term effect was 1.10 (95% CI 0.86,1.40). The studies were not judged to be free from bias, and there was evidence of funnel plot asymmetry with larger studies showing smaller effects. The heterogeneity between studies was not explained by the technique used. Acupuncture was less effective than NRT. There was no evidence that acupuncture is superior to psychological interventions in the short- or long-term. There is limited evidence that acupressure is superior to sham acupressure for short-term outcomes (three trials, n = 325, RR 2.54, 95% CI 1.27,5.08), but no trials reported long-term effects. The pooled estimate for studies testing an intervention that included continuous auricular stimulation suggested a short-term benefit compared to sham stimulation (14 trials, n = 1155, RR 1.69, 95% CI 1.32,2.16); subgroup analysis showed an effect for continuous acupressure (seven studies, n = 496, RR 2.73, 95% CI 1.78,4.18) but not acupuncture with indwelling needles (six studies, n = 659, RR 1.24, 95% CI 0.91,1.69). At longer follow-up the CIs did not exclude no effect (five trials, n = 570, RR 1.47, 95% CI 0.79,2.74). The evidence from two trials using laser stimulation was inconsistent and could not be combined. The combined evidence on electrostimulation suggests it is not superior to sham electrostimulation (short-term abstinence: six trials, n = 634, RR 1.13, 95% CI 0.87,1.46; long-term abstinence: two trials, n = 405, RR 0.87, 95% CI 0.61,1.23). The authors concluded that although pooled estimates suggest possible short-term effects, there is no consistent, bias-free evidence that acupuncture, acupressure, or laser therapy have a sustained benefit on smoking cessation for six months or more while electrostimulation is not effective for smoking cessation. [111,Level I]

c. Meditation-based intervention

Carim-Todd, Mitchell and Oken (2013) conducted a systematic review to assess the efficacy of yoga and other meditation-based interventions for smoking cessation. Fourteen clinical trials met the inclusion criteria defined for this review. Each article was reviewed thoroughly, and evaluated for quality, design, and methodology. Although primary outcomes differed between studies, the fourteen articles, most with some limitations, reported promising effects supporting further investigation of the use of these practices to improve smoking cessation. The authors concluded that yoga and meditation-based therapies may assist smoking cessation. However, the small number of studies available and associated methodological problems require more clinical trials with larger sample sizes and carefully monitored interventions to determine rigorously if yoga and meditation are effective treatments.[112,Level I]

6.2 SAFETY

Eleven articles (studies) related to the safety of interventions for quit smoking met the inclusion criteria and included in this review.

Assessment of Risk of Bias

Assessment of risk of bias of cohort (CASP)[24]

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Harte & Merson[116]	+	?	+	+	+
Thomas et al[118]	+	+	+	?	?

Assessment of risk of bias of systematic review (CASP)

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Thomas et al[114]	+	+	+	?
Mills et al.[115]	+	?	+	-
Tonstad et al[117]	+	+	+	+
Dhippayom et al[119]	+	+	+	?
Leung et al.[120]	+	+	+	?

Assessment of risk of bias of RCT (Cochrane)

Criteria assessed	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Floden et al[113]	?	?	+	+	+	?
Allen et al.[121]	?	-	+	+	?	?

Assessment of risk of bias of pre-post studies with no control[27]

Criteria assessed	Cui et al[122]
Question or objective clearly stated?	+
Eligibility/selection criteria for study population clearly described?	+
Were participants representative for those who would be eligible for the test/ service/intervention in the population of interest?	?
Were all eligible participants that met the prespecified entry criteria enrolled?	?
Sample size sufficiently large to provide confidence in findings?	?
Test/service/intervention clearly described and delivered consistently?	+
Outcome measures prespecified, valid, reliable, and assessed consistently?	+
People assessing the outcome measures blinded to participants exposure/ interventions?	+
Loss to follow-up after baseline 20% or less? Loss to follow-up accounted for in the analysis?	+
Statistical methods examine changes in outcome measures from before to after intervention? p value?	+
Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?	?
If intervention conducted at group level, did statistical analysis take into account of individual level data to determine effects at group level?	+

As mentioned previously, Anthenelli et al. (2016) compared the relative neuropsychiatric safety risk and efficacy of varenicline and bupropion with nicotine patch and placebo in smokers with and without psychiatric disorders

in a randomised, double-blind, triple-dummy, placebo-controlled and active-controlled (nicotine patch; 21 mg per day with taper) trial of varenicline (1 mg twice a day) and bupropion (150 mg twice a day). One of the primary endpoint was the incidence of a composite measure of moderate and severe neuropsychiatric adverse events. All participants randomly assigned were included in the efficacy analysis and those who received treatment were included in the safety analysis. A total of 8144 participants were randomly assigned, 4116 to the psychiatric cohort (4074 included in the safety analysis) and 4028 to the non-psychiatric cohort (3984 included in the safety analysis). In the non-psychiatric cohort, 13 (1.3%) of 990 participants reported moderate and severe neuropsychiatric adverse events in the varenicline group, 22 (2.2%) of 989 in the bupropion group, 25 (2.5%) of 1006 in the nicotine patch group, and 24 (2.4%) of 999 in the placebo group. The varenicline–placebo and bupropion–placebo risk differences (RDs) for moderate and severe neuropsychiatric adverse events were −1.28 (95% CI −2.40 to −0.15) and −0.08 (95% CI −1.37 to 1.21), respectively; the RDs for comparisons with nicotine patch were −1.07 (95% CI −2.21 to 0.08) and 0.13 (95% CI −1.19 to 1.45), respectively. In the psychiatric cohort, moderate and severe neuropsychiatric adverse events were reported in 67 (6.5%) of 1026 participants in the varenicline group, 68 (6.7%) of 1017 in the bupropion group, 53 (5.2%) of 1016 in the nicotine patch group, and 50 (4.9%) of 1015 in the placebo group. The varenicline–placebo and bupropion–placebo RDs were 1.59 (95% CI −0.42 to 3.59) and 1.78 (95% CI −0.24 to 3.81), respectively; the RDs versus nicotine patch were 1.22 (95% CI −0.81 to 3.25) and 1.42 (95% CI −0.63 to 3.46), respectively. Across cohorts, the most frequent adverse events by treatment group were nausea (varenicline, 25% [511 of 2016 participants]), insomnia (bupropion, 12% [245 of 2006 participants]), abnormal dreams (nicotine patch, 12% [251 of 2022 participants]), and headache (placebo, 10% [199 of 2014 participants]). The study did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo. [50,Level I]

Floden et al. (2016) evaluated body mass index (BMI) changes in adolescents treated with bupropion SR for smoking cessation. This study reported changes in the BMI z-scores of adolescent smokers participating in a dose-ranging clinical trial of bupropion SR (150 mg/day and 300 mg/day) for smoking cessation. A total of 5296 adolescent smokers (placebo n=5100, 150 mg/day n=5101, 300 mg/day n=595) with a BMI z-score of 0.5 (SD 1.4), 0.5 (SD 1.3), and 0.5 (SD 1.2) in the placebo, 150 mg/day, and 300 mg/day groups, respectively, were followed for six months. Adolescents in the 300 mg/day group had a significant reduction in BMI z-score six weeks after quitting (95% CI (20.29, 20.04), p<0.01). This result was not sustained at the six-month follow-up. The authors concluded that a reduction in BMI z-score during smoking cessation with bupropion has important implications for the future of adolescent smoking cessation. These results are particularly relevant for adolescents who have either overweight or obesity or who have reservations about quitting for fear of gaining weight or BMI. [113, level II-1]

Thomas et al. (2015) examined the risk of neuropsychiatric adverse events associated with varenicline compared with placebo by conducting a systematic review and meta-analysis. Randomised controlled trials with a placebo comparison group that reported on neuropsychiatric adverse events (depression, suicidal ideation, suicide attempt, suicide, insomnia, sleep

disorders, abnormal dreams, somnolence, fatigue, anxiety) and death were considered. Studies that did not involve human participants, did not use the maximum recommended dose of varenicline (1 mg twice daily), and were cross over trials were excluded. In the 39 RCTs (10 761 participants), there was no evidence of an increased risk of suicide or attempted suicide (OR 1.67, 95% CI 0.33, 8.57), suicidal ideation (OR 0.58, 95% CI 0.28,1.20), depression (OR 0.96, 95% CI 0.75,1.22), irritability (OR 0.98, 95% CI 0.81,1.17), aggression (OR 0.91, 95% CI 0.52,1.59), or death (OR 1.05, 95% CI 0.47, 2.38) in the varenicline users compared with placebo users. Varenicline was associated with an increased risk of sleep disorders (OR 1.63, 95% CI 1.29,2.07), insomnia (OR 1.56, 95% CI 1.36,1.78), abnormal dreams (OR 2.38, 95% CI 2.05,2.77), and fatigue (OR 1.28, 95% CI 1.06,1.55) but a reduced risk of anxiety (OR 0.75, 95% CI 0.61,0.93). Similar findings were observed when risk differences were reported. There was no evidence for a variation in depression and suicidal ideation by age group, sex, ethnicity, smoking status, presence or absence of psychiatric illness, and type of study sponsor (that is, pharmaceutical industry or other). The study found no evidence of an increased risk of suicide or attempted suicide, suicidal ideation, depression, or death with varenicline. There was evidence that varenicline was associated with a higher risk of sleep problems such as insomnia and abnormal dreams. These side effects, however, are already well recognised.[114,Level I]

Mills et al. (2014) evaluated cardiovascular events associated with smoking cessation pharmacotherapies in a network meta-analysis. They examined whether three licensed smoking cessation therapies - NRT, bupropion, and varenicline are associated with an increased risk of cardiovascular disease events.They included any RCT of the three treatments that reported cardiovascular disease outcomes. Among 63 eligible RCTs involving 21 NRT RCTs, 28 bupropion RCTs, and 18 varenicline RCTs, the authors found no increase in the risk of all cardiovascular disease events with bupropion (RR 0.98, 95% CI 0.54,1.73) or varenicline (RR 1.30, 95% CI 0.79,2.23). There was an elevated risk associated with NRT that was driven predominantly by less serious events (RR, 2.29, 95% CI 1.39,3.82). When the authors examined major adverse cardiovascular events, they found a protective effect with bupropion (RR 0.45, 95% CI 0.21,0.85) and no clear evidence of harm with varenicline (RR, 1.34, 95% CI 0.66,2.66) or NRT (RR 1.95, 95% CI, 0.26,4.30). The authors concluded that smoking cessation therapies do not appear to raise the risk of serious cardiovascular disease events.[115, Level I]

Harte and Meston (2014) evaluated the effects of smoking cessation involving a nicotine transdermal patch treatment on heart rate variability among long-term male smokers. Cigarette smoking has been shown to adversely affect heart rate variability (HRV), suggesting dysregulation of cardiac autonomic function. Conversely, smoking cessation is posited to improve cardiac regulation. Sixty-two healthy male smokers enrolled in an 8-week smoking cessation program. Participants were assessed at baseline (while smoking regularly), at mid-treatment (while using a high-dose patch), and at follow-up, four weeks after patch discontinuation. Both time-domain (standard deviation of normal-to-normal (NN) intervals (SDNN), square root of the mean squared difference of successive NN intervals (RMSSD), and percent of NN intervals for which successive heartbeat intervals differed by at least 50 ms (pNN50) and frequency-domain (low frequency (LF), high frequency (HF), LF/HF ratio) parameters of HRV were assessed at each visit. Successful quitters (n=20),

compared to those who relapsed (n=42), displayed significantly higher SDNN, RMSSD, pNN50, LF, and HF at follow-up, when both nicotine and smoke free. The study concluded that smoking cessation significantly enhances HRV in chronic male smokers, indicating improved autonomic modulation of the heart. It suggested that these findings may be primarily attributable to nicotine discontinuation rather than tobacco smoke discontinuation alone.[116, Level II-3]

In a systematic review, Tonstad et al. (2014) aimed to determine the incidence and severity of nicotine-related adverse events in subjects with levels of cotinine, a metabolite of nicotine, that increased by more than 50%, compared with baseline smoking in controlled clinical trials of NRT. Data from participants in randomised, double-blind, controlled trials of various formulations of NRT (Nicorette®) including patch, gum, oral inhaler, sublingual tablet, nasal spray, mouth spray, and combinations were extracted from a clinical database. In addition to baseline, at least one subsequent plasma or salivary cotinine concentration was measured, and adverse events were recorded simultaneously. Of 28 eligible studies, 24 were smoking cessation studies, and 4 were smoking reduction studies. Cotinine levels that increased by >50% above baseline were recorded during treatment in 746 of 7,120 subjects (10.5%). Nausea was reported in 16 subjects (0.2% of the total, upper 99% confidence limit [CL] 0.4%), vomiting in 2 subjects (0.0%, upper 99% CL 0.1%), palpitations in 5 subjects (0.1%, upper 99% CL 0.2%), dizziness in 11 subjects (0.2%; upper 99%CL 0.3%), and headache in 35 subjects (0.5%, upper 99% CL 0.7%). The authors concluded that typical symptoms indicating nicotine overdose together with high cotinine levels were rare during treatment with NRT. These findings support the safety of NRT for smoking cessation or reduction.[117, Level I]

Thomas et al. (2013) compared the risk of depression, suicide, and self-harm in patients prescribed varenicline or bupropion with those prescribed NRT in a prospective cohort study within the Clinical Practice Research Datalink. A total of 349 general practices in England involving 119,546 men and women aged 18 years and over who used a smoking cessation product participated in the study. There were 81 545 users of nicotine replacement products (68.2% of all users of smoking cessation medicines), 6741 bupropion (5.6%), and 31,260 varenicline (26.2%) users. Outcomes included treated depression and fatal and non-fatal self-harm within three months of the first smoking cessation prescription, determined from linkage with mortality data from the Office for National Statistics (for suicide) and Hospital Episode Statistics data (for hospital admissions relating to non-fatal self-harm). Hazard ratios or risk differences were estimated using Cox multivariable regression models, propensity score matching, and instrumental variable analysis using physicians' prescribing preferences as an instrument. Sensitivity analyses were performed for outcomes at six and nine months. A total of 92 cases of fatal and non-fatal self-harm (326.5 events per 100,000 person-years) and 1094 primary care records of treated depression (6963.3 per 100,000 person-years) were reported. Cox regression analyses showed no evidence that patients prescribed varenicline had higher risks of fatal or non-fatal self-harm (HR 0.88, 95% CI 0.52,1.49) or treated depression (HR 0.75, 95% CI 0.65, 0.87) compared with those prescribed NRT. There was no evidence that patients prescribed bupropion had a higher risk of fatal or non-fatal self-harm (HR 0.83, 95% CI 0.30, 2.31) or of treated depression (HR 0.63, 95% CI 0.46, 0.87) compared with patients prescribed NRT. Similar findings were obtained using propensity score methods and instrumental variable analyses. There is

no evidence of an increased risk of suicidal behaviour in patients prescribed varenicline or bupropion compared with those prescribed NRT. These findings should be reassuring for users and prescribers of smoking cessation medicines.[118,Level II-3]

Dhippayom et al. (2011) conducted a systematic review and meta-analysis on the safety of nortriptyline at doses equivalent to those used in aiding smoking cessation. A systematic search of relevant articles in major databases was done and all studies of nortriptyline at doses between 75 and 100mg in any indication were reviewed. From 442 potentially relevant articles identified, 17 studies met the selection criteria and were included for data analysis. Indications for nortriptyline in these studies were smoking cessation (eight studies), depression (five studies), neuropathic pain (three studies) and schizophrenia (one study). 2885 individuals participated in these studies, with exposure time ranging between 4 and 12 weeks. The major comparator used in these trials was placebo. Overall, no life-threatening events occurred in these studies. Orthostatic hypotension was significantly higher in nortriptyline users than in comparator groups (RR 2.8, 95% CI 1.4, 5.3). Other adverse events significantly associated with nortriptyline were anticholinergic-related effects including drowsiness, dizziness, gastrointestinal disturbance and dysgeusia. The evidence suggests that nortriptyline, at doses between 75 and 100 mg, is not significantly associated with serious adverse events when administered in patients without underlying cardiovascular disease.[119,Level I]

Leung et al. (2011) evaluated the gastrointestinal adverse effects of varenicline at maintenance dose through a meta-analysis of RCTs. Selected studies satisfied the following criteria: (i) duration of at least six weeks, (ii) titrated dose of varenicline for seven days then a maintenance dose of 1 mg twice-per-day, (iii) randomised placebo-controlled design, (iv) extractable data on adverse event - nausea, constipation or flatulence. A total of 98 potentially relevant studies were identified, 12 of which met the final inclusion criteria (n = 5114). All 12 studies reported adverse events on nausea, which led to an OR of 4.45 (95% CI = 3.79-5.23, $p < 0.001$; I^2 =0.06%, CI = 0%-58.34%) and a NNH of 5. Eight studies (n = 3539) contain data on constipation pooled into an OR of 2.45 (95% CI = 1.61-3.72, $p < 0.001$; I^2 = 34.09%, CI = 0%-70.81%) with a NNH of 24. Finally, five studies (n =2516) reported adverse events of flatulence, which pooled an OR of 1.74 (95% CI = 1.23-2.48, p = 0.002; I^2 = 0%, CI = 0%- 79.2%) with a NNH of 35. The authors concluded that the use of varenicline at maintenance dose of 1 mg twice a day for longer than six weeks is associated with adverse gastrointestinal effects. For every 5 treated subjects, there will be an event of nausea, and for every 24 and 35 treated subjects, an event of constipation and flatulence is expected respectively. Family physicians should counsel patients of such risks accordingly during their maintenance therapy with varenicline.[120, Level I]

Allen et al. assessed the effect of nicotine patch on energy intake and weight gain in postmenopausal women during smoking cessation. Postmenopausal women who smoked ≥10 cigarettes/day were enrolled in this double-blind randomised placebo-controlled study. They were randomised to receive 21 mg nicotine or placebo patch for 12 weeks. Total energy intake (via four-day food diaries), body mass index (BMI; kg/m2), cigarettes/day and smoking status (self-report verified by exhaled carbon monoxide) were assessed at three time points: two weeks prior to quit date, 12 weeks after quit date, and 12 months after smoking cessation treatment. A total of 119 participants on

average, 55.8 (SD 6.7) years old with a baseline BMI of 27.0 (SD 5.2) and average cigarette/day were 21.1 (SD 8.6). At Week 12, participants randomised to nicotine patch increased their mean caloric intake by 146.4 (SD 547.7) kcal/day where as those on placebo patch decreased their caloric intake by 175.3 (SD 463.2, f-value = 10.1, p-value = 0.002). Despite the differences in caloric intake, body weight remained similar between groups. The results of this study indicate that nicotine patch may increase energy intake during treatment, and does not prevent post-cessation weight gain in postmenopausal smokers. Additional research is needed to replicate these findings and assess whether different forms of NRT influence caloric intake and post-cessation weight gain in postmenopausal smokers.[121, level I]

Cui et al. examined the safety and tolerability of varenicline tartrate (Champix®/Chantix®) for smoking cessation in HIV-infected subjects. In this multicenter pilot open label study, varenicline 1.0 mg was used twice daily for 12 weeks with dose titration in the first week. Adverse events (AEs) during the treatment period were recorded. Changes from baseline in laboratory tests, vital signs, daily cigarette consumption, nicotine dependence, and withdrawal were measured through week 24. Self-reported abstinence was validated by serum cotinine at week 12. A total of 36 subjects with a mean of 29 pack-years of smoking and a minimum of 4 cigarettes per day were enrolled. All but 1 were male, 33 (92%) were white. The most frequently reported AEs were nausea (33%), abnormal dreams (31%), affect lability (19%), and insomnia (19%). Six (17%) subjects discontinued varenicline due to AEs. No grade 3 or 4 laboratory abnormalities or serious AEs occurred during the study. There was no significant change in HIV viral load. CD4 counts increased by 69 cells/mm3 (p = 0.001) at week 24. Serum cotinine-verified 4-week continuous abstinence rate through weeks 9–12 was 42% (95% CI 26,58%). Adverse events and abstinence rates were comparable to those in published randomised controlled trials conducted in generally healthy HIV negative smokers. Varenicline was safe and appears effective among HIV-infected smokers in this exploratory study, although AEs were common. The most common AE was nausea, with no adverse effect on HIV treatment outcome. Close monitoring of liver enzymes and blood pressure is recommended for HIV-positive smokers taking varenicline.[122,level III]

6.3 COST- EFFECTIVENESS

Seventeen articles (studies) related to the cost-effectiveness of interventions for quit smoking met the inclusion criteria and included in this review.

Assessment of risk of bias of economic evaluation (CASP)

Criteria assessed	Cadier et al[123]	Essex et al[124]	Mullen et al.[125]	Richter et al[126]	Tosanguan & Saiyakumarn[127]	Xu et al[130]	Barnett et al[132]	Clayforth et al[129]	Von Wartburg et al[128]	Graham et al[131]	Oh et al.[133]	Lutz et al.[134]	Hoogendoorn et al[135]	Kotz et al[136]	Vemer et al[137]	Wang et al[20]	Heredia-Pi et al[138]
A well-define question posed?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Comprehensive description of competing alternative given?	+	?	+	?	+	?	?	+	+	+	?	+	+	?	+	?	?
Effectiveness established?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Effects of intervention identified, measured and valued appropriately?	+	?	+	+	+	+	+	?	+	+	+	+	+	+	+	?	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	?	+	?	+	+	+	?	?	+	+	+	+	?	+	+	?	+
Costs and consequences adjusted for different times at which they occurred (discounting)?	+	+	+	+	+	+	+	?	+	?	+	+	+	+	+	+	+
Results of the evaluation?	+	+	+	+	+	+	+	+	+	+	+	+	+	?	+	?	+
Incremental analysis of the consequences and costs of alternatives performed?	+	+	+	+	+	+	+	?	+	+	+	+	+	+	+	+	+
Sensitivity analysis performed?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+

Cadier et al. (2016) estimated the incremental cost-effectiveness ratios (ICER) of providing free access to cessation treatment taking into account the cost offsets associated with the reduction of the three main diseases related to smoking: lung cancer, chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD). In order to measure the financial impact of such a measure they also conducted a probabilistic budget impact analysis. A cost-effectiveness analysis was conducted using a Markov state-transition model that compared free access to cessation treatment to the existing coverage of €50 provided by the French statutory health insurance, taking into account the cost offsets among current French smokers aged 15–75 years. The results were expressed by the incremental cost-effectiveness ratio in 2009 Euros per life year gained (LYG) at the lifetime horizon. They estimated a base case scenario and carried out a Monte Carlo sensitivity analysis to account for uncertainty. Assuming a participation rate of 7.3%, the ICER value for free access to cessation treatment was €3,868 per LYG in the base case. The variation of parameters provided a range of ICER values from -€736 to €15,715 per LYG. In 99% of cases, the ICER for full coverage was lower than €11,187 per LYG. The probabilistic budget impact analysis showed that the potential cost saving for lung cancer, COPD and CVD ranges from €15 million to €215 million at the five-year horizon for an initial cessation treatment cost of €125 million to €421 million. The results suggest that providing medical support to smokers in their attempts to quit is very cost-effective and may even result in cost savings.[123, Level I]

Essex et al. (2015) evaluated cost-effectiveness of nicotine patches for smoking cessation in pregnancy (SNAP trial). A cost-effectiveness analysis was undertaken alongside the smoking, nicotine, and pregnancy trial to compare NRT patches plus behavioral support to behavioural support alone, for pregnant women who smoked. At delivery, biochemically verified quit rates were slightly higher at 9.4% in the NRT group compared to 7.6% in the control group (OR 1.26, 95% CI 0.82,1.96), at an increased cost of around £90 per participant. Higher costs in the NRT group were mainly attributable to the cost of NRT patches (mean = £46.07). The incremental cost-effectiveness ratio associated with NRT was £4,926 per quitter and a sensitivity analysis including only singleton births yielded an ICER of £4,156 per quitter. However, wide confidence intervals indicated a high level of uncertainty. The authors concluded that without a specific willingness to pay threshold, and due to high levels of statistical uncertainty, it is hard to determine the cost-effectiveness of NRT in this population. Furthermore, future research should address compliance issues, as these may dilute any potential effects of NRT, thus reducing the cost-effectiveness.[124, Level I]

Mullen et al. (2015) conducted an economic evaluation of a hospital-initiated intervention for smokers with chronic disease, in Ontario, Canada. They modelled the cost-effectiveness of the Ottawa Model for Smoking Cessation (OMSC), an intervention that includes in-hospital counselling, pharmacotherapy and post-hospital follow-up, compared to usual care among smokers hospitalised with acute myocardial infarction (AMI), unstable angina (UA), heart failure (HF), and chronic obstructive pulmonary disease (COPD). A cost-effectiveness analysis was conducted based on a decision-analytic model to assess smokers hospitalised in Ontario, Canada for AMI, UA, HF, and COPD, their risk of continuing to smoke and the effects of quitting on rehospitalisation and mortality over a 1-year period. They calculated short-term and long-term cost-effectiveness ratios. The primary outcome was 1-

year cost per quality-adjusted life year (QALY) gained. From the hospital payer's perspective, delivery of the OMSC can be considered cost effective with 1-year cost per QALY gained of $C1386, and lifetime cost per QALY gained of $C68. In the first year, the provision of the OMSC to 15 326 smokers would generate 4689 quitters, and would prevent 116 rehospitalisations, 923 hospital days, and 119 deaths. Results were robust within numerous sensitivity analyses. The OMSC appears to be cost-effective from the hospital payer perspective. Important consideration is the relatively low intervention cost compared to the reduction in costs related to readmissions for illnesses associated with continued smoking.[125, Level I]

Richter et al. (2015) conducted comparative and cost effectiveness of delivering expert tobacco treatment at a distance: telemedicine counseling that was integrated into smokers' primary care clinics (Integrated Telemedicine—ITM) versus telephone counseling, similar to telephone quitline counseling, delivered to smokers in their homes. Smokers (n=566) were recruited offline from 20 primary care and safety net clinics across Kansas. They were randomly assigned to receive 4 sessions of ITM or 4 sessions of phone counseling. Patients in ITM received real-time video counseling, similar to Skype, delivered by computer/webcams in clinic exam rooms. Three full-time equivalent trained counselors delivered the counseling. The counseling duration and content was the same in both groups and was available in Spanish or English. Both groups also received identical materials and assistance in selecting and obtaining cessation medications. The primary outcome was verified 7-day point prevalence smoking abstinence at month 12, using an intent-to-treat analysis. There were no significant baseline differences between groups, and the trial achieved 88% follow-up at 12 months. Verified abstinence at 12 months did not significantly differ between ITM and phone (9.8%, 27/280 vs 12%, 34/286; p=0.406). Phone participants completed somewhat more counseling sessions than ITM (mean 2.6, SD 1.5 vs mean 2.4, SD 1.5; p=0.083); however, participants in ITM were significantly more likely to use cessation medications than participants in phone (55.9%, 128/280 vs 46.1%, 107/286; p=0.03). Compared to phone participants, ITM participants were significantly more likely to recommend the programme to a family member or friend (p=0.0075). From the combined provider plus participant (societal) perspective, phone was significantly less costly than ITM. Participants in ITM had to incur time and mileage costs to travel to clinics for ITM sessions From the provider perspective, counseling costs were similar between ITM (US $45.46, SD 31.50) and phone (US $49.58, SD33.35); however, total provider costs varied widely depending on how the clinic space for delivering ITM was valued. Findings did not support the superiority of ITM over telephone counseling for helping rural patients quit smoking. ITM increased utilization of cessation pharmacotherapy and produced higher participant satisfaction, but phone counseling was significantly less expensive. [126, Level I]

Tosanguan and Chaiyakunapruk (2015) conducted a cost-effectiveness analysis of clinical smoking cessation interventions in Thailand. The study aimed to estimate the incremental cost-effectiveness ratio of a range of clinical smoking cessation interventions available in Thailand by using a Markov model, cost-effectiveness, in terms of cost per quality-adjusted life years (QALY) gained, from a range of interventions was estimated from a societal perspective for males and females aged 40 years who smoke at least ten cigarettes per day. Interventions considered were: counselling in hospital,

phone counselling (Quitline) and counselling plus nicotine gum, nicotine patch, bupropion, nortriptyline or varenicline. An annual discounting rate of 3% was used. Probabilistic sensitivity analyses were conducted and a cost-effectiveness acceptability curve (CEAC) plotted. Comparisons between interventions were conducted involving application of a 'decision rule' process. Counselling with varenicline and counselling with nortriptyline were found to be cost-effective. Hospital counselling only, nicotine patch and bupropion were dominated by Quitline, nortriptyline and varenicline, respectively, according to the decision rule. When compared with unassisted cessation, probabilistic sensitivity analysis revealed that all interventions have very high probabilities (95%) of being cost-saving except for NRT patch (74%). In middle-income countries such as Thailand, nortriptyline and varenicline appear to provide cost-effective clinical options for supporting smokers to quit.[127, level I]

Von Wartburg et al. (2014) conducted a long-term cost-effectiveness of varenicline (12-week standard course and 12 + 12-week extended course) versus other smoking cessation strategies in Canada using the Benefits of Smoking Cessation on Outcomes (BENESCO) model. Efficacy rates of the standard course (12 weeks) varenicline, extended course (12 + 12 weeks) varenicline, bupropion, NRT and unaided intervention were derived based on a published mixed treatment comparison methodology and analysed within a Markov cohort model to estimate their cost-effectiveness over the lifetime cycle. Study cohort, smoking rates and prevalence, incidence and mortality of smoking-related diseases were calibrated to represent the Canadian population. Over the subjects' lifetime, both the standard and the extended course of varenicline is shown to dominate (e.g. less costly and more effective) all other alternative smoking cessation interventions considered. Compared with the standard varenicline treatment course, the extended course is highly cost-effective with an incremental cost-effectiveness ratio (ICER) less than $4000 per quality-adjusted life year. Including indirect cost and benefits of smoking cessation interventions further strengthens the result with the extended course of varenicline dominating all other alternatives considered.[128, Level II-I]

Leaviss et al (2014) conducted an economic evaluation to estimate the cost-effectiveness of cytisine and varenicline for smoking cessation. The model structure was based on an existing and widely used model, the Benefits of Smoking Cessation on Outcomes (BENESCO) model which uses an annual cycle length and assumes that all smokers die at age 100 years, if death has not been simulated at an earlier age. Future costs and benefits were discounted at a rate of 3.5% per annum. A hypothetical cohort of 10,000 smokers enters the model, with each smoker assumed to make a single quit attempt, assisted by either varenicline or cytisine with four of the health states as either acute (CHD and stroke) or chronic (COPD and lung cancer) conditions. Perspective was that of the UK NHS for costs and health effects on the individual for outcomes, in line with National Institute for Health and Care Excellence (NICE) guidance. The intervention was standard 25-day course of cytisine; six 1.5-mg tablets per day for 3 days (days 1–3), five tablets per day for 9 days (days 4–12), four tablets per day for 4 days (days 13–16), three tablets per day for 4 days (days 17–20), and two tablets per day for the final 5 days (days 21–25) in comparison to standard 12-week course of varenicline (500 µg once daily for 3 days, increased to 500 µg twice a day for 4 days, then 1mg twice a day for 11 weeks). Mean discounted total costs

per smoker for cytisine and varenicline were £4973 and £5225, respectively (incremental cost of –£251) while QALYs were calculated to be at 14.38 for cytisine and 14.35 for varenicline (incremental of 0.03). At any threshold of willingness to pay, up to £100,000 per QALY gained, cytisine was the optimal intervention in over 90% of the simulations within the probabilistic sensitivity analysis (PSA). This reflects the higher costs associated with varenicline treatment. As the willingness to pay increases, the probability that cytisine is preferable falls and the likelihood that varenicline is optimal rises. Given that cytisine was estimated to be the more effective treatment in 90% of simulations, the value for cytisine on the cost-effectiveness acceptability curve will asymptote at 90%. The assumed treatment cost for cytisine is lower than that for varenicline, but the cytisine cost estimate if adopted for use within the NHS is uncertain. In a threshold analysis it was estimated that the price of the cytisine regimen would have to rise to over £250 (from an estimate of £16.79, a greater than 14-fold rise) for the total expected lifetime cost with cytisine treatment to equal the total expected lifetime cost with varenicline treatment. The authors concluded that while cytisine is found to be more cost-effective than varenicline, the conclusion is uncertain and therefore, head-to-head trial of varenicline and cytisine is recommended. [58,Level I]

Clayforth et al. (2014) conducted a cost-effectiveness analysis of online, radio and print tobacco control advertisements targeting 25-39 year old males. Two testimonial advertisements featuring members of the target group were developed for radio, press and online media. Multiple waves of media activity were scheduled over a period of seven weeks, including an initial integrated period that included all three media and subsequent single media phases that were interspersed with a week of no media activity. The resulting quit website hits, quitline telephone calls, and registrations to online and telephone counselling services were compared to advertising costs to determine the relative cost-effectiveness of each media in isolation and the integrated approach. The online-only campaign phase was substantially more cost-effective than the other phases, including the integrated approach. This finding is contrary to the current assumption that the use of a consistent message across multiple media simultaneously is the most cost-effective way of reaching and affecting target audiences. Online advertising may be a highly cost-effective channel for low-budget tobacco control media campaigns.[129, Level II-2]

Xu et al. (2013) conducted a cost-effectiveness analysis of the first federally funded national mass anti-smoking campaign launched in 2012. The “Tips From Former Smokers®” (Tips®) campaign resulted in a 12% relative increase in the U.S population-level quit attempts. The CEA was conducted from a funding agency’s perspective. Estimates of sustained cessations; premature deaths averted; undiscounted life years (LYs) saved; and quality-adjusted life years (QALYs) gained by Tips® were estimated. Tips® saved about 179,099 QALYs and prevented 17,109 premature deaths in the U.S. With the campaign cost of roughly $48 million, it spent approximately $480 per quitter, $2,819 per premature death averted, $393 per LY saved, and $268 per QALY gained. Tips® was not only successful at reducing smoking-attributable morbidity and mortality but also was a highly cost-effective mass media intervention.[130, Level II-2]

Graham et al. (2013) evaluated the cost-effectiveness of internet and telephone treatment for smoking cessation of the iQUITT Study. The iQUITT Study, is a randomised trial comparing basic internet, enhanced internet and enhanced internet plus telephone counselling at three, six, 12 and 18 months. Payer perspective was used to evaluate the average and incremental cost per quitter of the three interventions using intention-to-treat analysis of 30-day single-point prevalence and multiple-point prevalence (MPP) abstinence rates. They also examined results based on adherence. Costs included commercial charges for each intervention. Discounting was not included given the short time horizon. Basic internet had the lowest cost per quitter at all time points. In the analysis of incremental costs per additional quitter, enhanced internet plus phone was the most cost-effective using both single and MPP abstinence metrics. As adherence increased, the cost per quitter dropped across all arms. Costs per quitter were lowest among participants who used the 'optimal' level of each intervention, with an average cost per quitter at three months of USD 7 for basic internet, USD 164 for enhanced internet and USD 346 for enhanced internet plus phone. The authors concluded that adherence to 'optimal' internet and combined internet and telephone interventions yields the highest number of quitters at the lowest cost. Cost-effective means of ensuring adherence to such evidence-based programmes could maximise their population-level impact on smoking prevalence.[131, Level I]

Barnett et al. (2012) estimated cost-effectiveness of extended cessation treatment for older smokers. Participants who completed a 12-week smoking cessation program were factorial randomised to extended cognitive behavioural treatment and extended NRT in a free-standing smoking cessation clinic. A total of 402 smokers aged 50 years and older were recruited from the community. The trial measured biochemically verified abstinence from cigarettes after 2 years and the quantity of smoking cessation services utilized. Trial findings were combined with literature on changes in smoking status and the age- and gender-adjusted effect of smoking on health-care cost, mortality and quality of life over the long term in a Markov model of cost-effectiveness over a lifetime horizon. The addition of extended cognitive behavioural therapy added $83 in smoking cessation services cost (p= 0.012, 95% CI $22,212). At the end of follow-up, cigarette abstinence rates were 50% with extended cognitive behavioural therapy and 37.2% without this therapy (p < 0.05, OR 1.69, 95% CI 1.18,2.54). The model-based incremental cost-effectiveness ratio was $6324 per quality-adjusted life year (QALY). Probabilistic sensitivity analysis found that the additional $947 in lifetime cost of the intervention had a 95% CI of −$331 to 2081; the 0.15 additional QALYs had a 95% CI of 0.035–0.280, and that the intervention was cost-effective against a $50 000/QALY acceptance criterion in 99.6% of the replicates. Extended NRT was not cost-effective. Adding extended cognitive behavior therapy to standard cessation treatment was cost-effective. [132, Level I]

Oh et al. (2012) determined cost and effectiveness of the nationwide government-supported smoking cessation clinics in the Republic of Korea. The cost of the service (staff salary, medication, education and promotion and overhead) was calculated from clinics' 2009 financial report. The number of service users, self-reported four-week and six-month quit rates and the proportion of NRT users were collected from the service's performance monitoring data. Long-term quit rate and life-years saved by quitting were estimated and used in addition to monitoring data to evaluate the

effectiveness of the service. A total of 354, 554 smokers used the smoking cessation clinics in 2009. The self-reported four-week and six-month quit rates were 78% and 40%, respectively. Estimated one-year and eight-year quit rates were 28.1% and 12.9%, respectively. The cost of the service in 2009 was USD 21,127. Cost per service user who set a quit date was USD 60. Cost per service user who maintained cessation at four weeks, six months and one year was USD 76, USD 149 and USD 212, respectively. When considering eight-year quit rates, the cost per life-year saved was estimated at USD 128 in the base scenario and increased to USD 230 in the worst-case scenario. The nationwide government-supported public health centre-based smoking cessation clinics provided highly cost-effective service at a level of 0.46% of the per capita gross domestic product.[133, Level I]

Lutz et al. (2012) performed cost analysis of varenicline versus bupropion, NRT, and unaided cessation in Nicaragua over five time horizons: two, five, ten, and 20 years, and lifetime. The current annual costs of chronic obstructive pulmonary disease, lung cancer, coronary heart disease, and stroke were estimated based on the current annual incidence for each disease using one public hospital database. The Benefits of Smoking Cessation on Outcomes (BENESCO) simulation model was used to obtain the projected direct costs for each strategy. An adult cohort (N = 3,639,948) from Nicaragua was used and the assessment was conducted using the health care payer's perspective. Costs were discounted at 5% annually. Probabilistic sensitivity analyses were conducted using a Monte Carlo second-order approach. Varenicline is associated with the highest health care cost-savings compared with the other three alternatives at five, ten and 20 years, and lifetime. At lifetime, varenicline would result in savings of USD 4,545,008, USD 5,859,300, and USD 11,033,221 when compared with bupropion, NRT, and unaided cessation, respectively. Varenicline also avoided the highest number of smoking-related deaths in comparison with the alternatives. At year ten, varenicline avoided 96, 124, and 234 more deaths than bupropion, NRT, and unaided cessation, respectively. The results of probabilistic sensitivity analyses support these findings. The use of a smoking cessation therapy with varenicline would generate long-term savings to Nicaragua's health care institutions of USD 11 million in the lifetime time horizon.[134,Level II-I]

Hoogendoorn et al. (2010) aimed to estimate the long-term cost-effectiveness of smoking cessation interventions for patients with chronic obstructive pulmonary disease by conducting a systematic review of RCTs. The different interventions were grouped into four categories: usual care, minimal counselling, intensive counselling and intensive counselling plus pharmacotherapy. For each category the average 12-month continuous abstinence rate and intervention costs were estimated. A dynamic population model for COPD was used to project the long-term cost- effectiveness (25 years) of one-year implementation of the interventions for 50% of the patients with COPD who smoked compared with usual care. Uncertainty and one-way sensitivity analyses were performed for variations in the calculation of the abstinence rates, the type of projection, intervention costs and discount rates. Nine studies were selected. The average 12-month continuous abstinence rates were estimated to be 1.4% for usual care, 2.6% for minimal counselling, 6% for intensive counselling and 12.3% for pharmacotherapy. Compared with usual care, the costs per quality-adjusted life year (QALY) gained for minimal counselling, intensive counselling and pharmacotherapy were €16,900, €8200

and €2400, respectively. The results were most sensitive to variations in the estimation of the abstinence rates and discount rates. Compared with usual care, intensive counselling and pharmacotherapy resulted in low costs per QALY gained with ratios comparable to results for smoking cessation in the general population. Compared with intensive counselling, pharmacotherapy was cost saving and dominated the other interventions.[135, Level I]

Kotz et al. (2010) evaluated how cost-effective is "No Smoking Day", an annual UK-wide campaign to encourage smokers to quit. Comparison of reported quit attempts in the month following NSD for three consecutive years with adjacent months using repeated national surveys of quit attempts. A total of 1309 adults who had smoked in the past year who responded to the surveys in the month following NSD and a comparison group of 2672 adults who smoked in the past year who responded to the survey in the two adjacent months participated in the study. The main outcome measures include the number of additional smokers who quit permanently in response to NSD estimated from the survey results. The incremental cost-effectiveness ratio (ICER) was calculated by combining this estimate with established estimates of life years gained and the known costs of NSD. The rate of quit attempts was 2.8 percentage points higher in the months following NSD (120/1309) compared with the adjacent months (170/2672; 95% CI 0.99%,4.62%), leading to an estimated additional 0.07% of the 8.5 million smokers in England quitting permanently in response to NSD. The cost of NSD per smoker was £0.088. The discounted life years gained per smoker in the modal age group 35 to 44 years was 0.00107, resulting in an ICER of £82.24 (95% CI 49.7,231.6). ICER estimates for other age groups were similar. In conclusion, NSD emerges as an extremely cost-effective public health intervention.[136, Level II-2]

Vemer et al. (2010) conducted a cost-utility of reimbursing smoking cessation support in the Netherlands. The short-term efficiency of reimbursement has been evaluated previously. However, a thorough estimate of the long-term cost–utility is lacking. Results from a randomised controlled trial were extrapolated to long-term outcomes in terms of health care costs and (quality adjusted) life years (QALY) gained, using the Chronic Disease Model. The first scenario was no reimbursement. In a second scenario, the short-term cessation rates from the trial were extrapolated directly. Sensitivity analyses were based on the trial's confidence intervals. In the third scenario the additional use of SCS as found in the trial was combined with cessation rates from international meta-analyses. Intervention costs per QALY gained compared to the reference scenario were approximately €1200 extrapolating the trial effects directly, and €4200 when combining the trial's use of SCS with the cessation rates from the literature. Taking all health care effects into account, even costs in life years gained, resulted in an estimated incremental cost–utility of €4500 and €7400, respectively. In both scenarios costs per QALY remained below €16 000 in sensitivity analyses using a life-time horizon. Extrapolating the higher use of SCS due to reimbursement led to more successful quitters and a gain in life years and QALYs. Accounting for overheads, administration costs and the costs of SCS, these health gains could be obtained at relatively low cost, even when including costs in life years gained. Hence, reimbursement of SCS seems to be cost-effective from a health care perspective.[137, level I]

As previously mentioned, Wang et al. (2008) evaluated “Cut down to quit” (CDTQ) with nicotine replacement therapies in smoking cessation in a systematic review of effectiveness and economic analysis. Meta-analyses of the study level results demonstrated statistically significant superiority of NRT compared with placebo. From this meta-analysis indicated statistically significant superiority of NRT versus placebo (RR 2.06, 95% CI 1.34 ,3.15). The number needed to treat was 29. A *de novo* decision analytic model was constructed to estimate the cost effectiveness of making CDTQ with NRT available for smokers unwilling or unable to attempt an abrupt quit. The outcome measure was expected quality-adjusted life-years (QALYs). The model results suggest that CDTQ with NRT delivers incremental cost-effectiveness ratios (ICERs) ranging from around £1500/QALY to £7700/QALY depending on the age at which smoking cessation was achieved and the modes of CDTQ delivery. Assuming applicability to a single population, CDTQ was not cost-effective compared with abrupt quitting. If CDTQ with NRT were to be offered on the NHS as a matter of policy, the base-case results suggest that it would only be effective and cost-effective if a substantial majority of the people attempting CDTQ with NRT were those who would otherwise make no attempt to quit. This result is robust to considerable variation in the forms of CDTQ with NRT offered, and to the assumptions about QALY gained per quit success. The modelling undertaken, which was based on reasonable assumptions about costs, benefits and success rates, suggest that CDTQ is highly cost-effective compared with no quit attempt. CDTQ remains cost-effective if dilution from abrupt quitting forms a small proportion of CDTQ attempts. In an alternative analysis in which smokers who switch from an abrupt quit to CDTQ retain the success rate of abrupt quitters, all forms of CDTQ appear cost-effective. Randomised trials in recalcitrant smokers allowing head-to-head comparison of CDTQ delivered with various modalities would be informative.[20,Level I]

Heredia-Pi et al. (2012) estimated the maximum willingness to pay (WTP) for an effective smoking cessation treatment among smokers in Mexico and to identify the environmental, demographic, and socioeconomic factors associated with the WTP. A cross-sectional study was conducted. The sample contained 777 smokers who had responded to the 2009 Global Adult Tobacco Survey conducted in Mexico. Statistical associations and descriptive analyses were conducted to describe smokers and their WTP by using tobacco-related environmental, socioeconomic, and demographic variables. Overall, 74.4% of the smokers were men and 51.4% were daily smokers. On average, the smokers had been consuming tobacco for more than 15 years, 58.6% had made cessation attempts in the past, and around 10.0% knew about the existence of centers to aid in smoking cessation. The average WTP for an effective cessation method was USD191. Among men, the WTP was USD152 lower than among women. In all the estimated models, the higher an individual’s education and socioeconomic level, the higher his or her WTP. This study suggests that Mexican smokers interested in quitting smoking attribute a high monetary value ton effective cessation method. Male smokers demonstrated less altruistic behavior than did female smokers. Mexico requires the implementation of more policies designed to support smoking cessation and to limit tobacco addiction. [138, Level III]

6.4 ETHICAL / LEGAL / ORGANIZATIONAL ISSUES

Twelve articles (studies) related to the organizational issues for quit smoking met the inclusion criteria and included in this review.

a. Adherence to pharmacotherapies

In a systematic review, Hollands et al. (2015) aimed to determine the effectiveness of interventions designed specifically to increase medication adherence. Such interventions may include further educating individuals about the value of taking medications and providing additional support to overcome problems with maintaining adherence. The primary objective of this review was to assess the effectiveness of interventions to increase adherence to medications for smoking cessation, such as NRT, bupropion, nortriptyline and varenicline (and combination regimens). This was considered in comparison to a control group, typically representing standard care. Secondary objectives were to i) assess which intervention approaches are most effective; ii) determine the impact of interventions on potential precursors of adherence, such as understanding of the treatment and efficacy perceptions; and iii) evaluate key outcomes influenced by prior adherence, principally smoking cessation. Randomised, cluster-randomised or quasi-randomised studies in which participants using active pharmacological treatment for smoking cessation are allocated to an intervention arm or a control arm were considered. Eligible participants were smokers aged more than 18 years. Eligible interventions comprised any intervention that differed from standard care, and where the intervention content had a clear principal focus on increasing adherence to medications for tobacco dependence. Acceptable comparison groups were those that provided standard care, which depending on setting may comprise minimal support or varying degrees of behavioural support. Included studies used a measure of adherence behaviour that allowed some assessment of the degree of adherence. Eight studies involving 3,336 randomised participants were included. The interventions were all additional to standard behavioural support and typically provided further information on the rationale for, and emphasised the importance of, adherence to medication, and supported the development of strategies to overcome problems with maintaining adherence. The authors concluded that there is some evidence that interventions that devote special attention to improving adherence to smoking cessation medication through providing information and facilitating problem-solving can improve adherence, though the evidence for this is not strong and is limited in both quality and quantity. There is some evidence that such interventions improve the chances of achieving abstinence but again the evidence for this is relatively weak.[139,] Level I

Lam et al. (2005) investigated the factors associated with quitting and adherence to NRT use amongst Chinese smokers in Hong Kong. Chinese smokers (1186) who attended the Smoking Cessation Health Centre from August 2000 through January 2002 were studied. Trained counsellors provided individual counselling and carried out follow-up interviews. The authors used structured questionnaires at baseline and at one, three and 12 months and an intention-to-treat approach for analysis. Among those who received NRT (1051/1186), the prevalence of adherence (self-reported NRT use for at least 4 weeks) was 16% (95% CI 14%,18%). The 7-day point prevalence quit rate at 12 months (not smoking any cigarette during the past

seven days at the 12 month follow-up) was 27% (95% CI, CI 24%,29%). Stepwise logistic regression model showed that adherence to NRT use, a higher income, good perceived health and having more confidence in quitting were significant predictors of quitting. The quit rate in the adherent group (40%) was greater than that of the non-adherent group (25%; p<0.001). Older age, male, higher education, experience of NRT use, perceiving quitting as more difficult and willingness to pay were significant predictors of adherence. Clinically significant smoking cessation rates can be achieved among Chinese smokers in a clinic-based smoking cessation service. The NRT adherence was low and low adherence was associated with a lower quit rate. Trials of interventions to improve adherence and increase quit rates are needed.[140, Level II-2]

b. Acceptability and feasibility of various smoking cessation techniques

Haines-Saah et al. (2015) aimed to determine the feasibility of engaging young adults in participating in user-driven, online forums intended to provide peer support and motivate critical reflection about tobacco use and cessation among this high-use, hard-to-reach population. Picture Me Smokefree is an online tobacco reduction and cessation intervention for young adults that uses digital photography and social networking. A total of 60 young adults ages 19-24 years who self-identified as current cigarette smokers or who had quit within the last year were recruited from across British Columbia, Canada, and participated in an online photo group on Facebook over a period of 12 consecutive weeks. A variety of data collection methods were used including tracking online activity, a brief online follow-up survey, and qualitative interviews with study participants. Data analysis involved descriptive statistics on recruitment, retention, and participation and qualitative (e.g., narrative analysis, synthesis of feedback) feedback about participant engagement. Findings from this study suggest good potential for Facebook as an accessible, low-cost platform for engaging young adults to reflect on the reasons for their tobacco use, the benefits of quitting or reducing, and the best strategies for tobacco reduction. Young adults' frequent use of mobile phones and other mobile devices to access social networking permitted ease of access and facilitated real-time peer-to-peer support across a diverse group of participants. However, the study suggests that working with young tobacco users can be accompanied by considerable recruitment, participation, and retention challenges. There were differences in how young women and men engaged the photo-group intervention that should be considered, bearing in mind that in follow-up interviews participants indicated their preference for a mixed gender and "gender neutral" group format. Tobacco interventions for youth and young adults should be embedded within the existing social networking platforms they access most frequently, rather than designing a stand-alone online prevention or intervention resource. This subpopulation would likely benefit from tobacco reduction interventions that are gender-sensitive rather than gender-specific.[141, Level III]

Neuner-Jehle et al. (2013) examined the feasibility and acceptance of a smoking cessation counselling tool with different cardiovascular risk communication formats including graphs, in comparison with the International Primary Care Respiratory Group (IPCRG) 'quit smoking assistance' tool. The general practitioners were randomised into an intervention group (using communication tool in addition to the IPCRG sheet) and a control group

(using the IPCRG sheet only). Participants were asked for socioeconomic data, smoking patterns, understanding of information, motivation, acceptance and feasibility, and measured the duration and frequency of counselling sessions. Twenty-five GPs performed 2.8 counselling sessions per month in the intervention group and 1.7 in the control group (p=0.3) with 114 patients. The median duration of a session was ten minutes (control group 11 minutes, p=0.09 for difference). Median patients' motivation for smoking cessation was seven on a 10-point visual analogue scale with no significant difference before and after the intervention (p=0.2) or between groups (p=0.73 before and p=0.15 after the intervention). Median patients' ratings of motivation, self-confidence, understanding of information, and satisfaction with the counselling were 3-5 on a 5-point Likert scale, similar to GPs' ratings of acceptance and feasibility, with no significant difference between groups. Among Swiss GPs and patients, both communication tool and the IPCRG tool were well accepted and both merit further dissemination and application in research.[142, Level II-3]

Ybarra et al. (2013) investigated the feasibility of cell phone-based smoking cessation programs in lower income countries that have higher smoking prevalence rates. A one-arm feasibility and acceptability pilot study of SMS Turkey, a text messaging-based smoking cessation program, was conducted in Ankara, the capital of Turkey. The authors recruited 75 daily smokers who were seriously thinking about quitting in the subsequent 30 days into the six-week SMS Turkey program. Recruitment was completed in four months. Participant retention was high; almost all (96%) completed the program, and 84% provided 12-week follow-up data. Most (89%) of the respondents who completed the four-week follow-up measures (n = 38, 51%) said that the text messages were easy to understand and referred to what they were experiencing and feeling during the quitting process (78%). On the basis of intention to treat, 13% of participants (n = 10) reported, at 12-week follow-up, continuous abstinence since their quit date, confirmed by CO readings. The cell phone text messaging-based smoking cessation intervention appears feasible and acceptable in Ankara, Turkey.[143, level III]

Girgis et al. (2011) conducted a randomised controlled trial designed to evaluate the feasibility, acceptability and impact of a culturally specific cessation intervention delivered in the context of primary medical care in the most culturally diverse region of New South Wales. Adult Arabic smokers were recruited from practices of 29 general practitioners (GPs) in south-west Sydney and randomly allocated to usual care (n=194) or referred to six sessions of smoking cessation telephone support delivered by bilingual psychologists (n=213). Although 62.2% of participants indicated that telephone support would benefit Arabic smokers, there were no significant differences at six or 12 months between intervention and control groups in point prevalence abstinence rates (11.7% vs 12.9%, p=0.83; 8.4% vs 11.3%, p=0.68, respectively) or the mean shift in stage-of-change towards intention to quit. [144, level II-2]

Bentz et al. (2006) evaluated the feasibility of connecting patients in primary care settings to state-level quit lines. An observational study describing two methods (fax referral and providing a brochure) to connect private physician offices with a state-level quit line in Oregon. This study describes the resources required to create a clinical pathway for the 5A's in primary care (ask, advise, assess, assist, and arrange) using a state-level telephone quit

line as an intervention for cessation in primary care clinics sharing a common electronic medical record system, focusing on the costs and generalizability of this approach. Of the 15,662 smokers identified in 19 primary care clinics, 745 patients were referred to the Oregon Tobacco Quit Line during the study period. The program cost in the first year was $15 to $22 per patient connected with the quit line; in subsequent years, the cost decreased to $4 to $6 per quit-line connection. Connecting private physician offices to a state-level quit line is feasible, can be accomplished at low cost with minimal use of resources, and may be cost effective. Regional, state, and local tobacco quit lines should consider a physician office "quit-line connection" as a practical approach to increase utilization.[145, Level III]

c. Training

Verbiest et al. (2014) examined the effectiveness of low-intensity, practice-tailored training for general practitioners (GPs) aimed at personal and organizational barriers that arise when routinely asking patients' smoking status, advising to quit, and arranging follow-up. A cluster-randomised controlled trial with 49 GPs and 3,401 patients (677 smokers) was conducted. Two patient groups participated: 2,068 patients (433 smokers) at baseline and 1,333 patients (244 smokers) post intervention. At follow-up, 225 smokers of both groups participated. The primary outcome was GP smoking cessation counselling (asking about smoking status, advising to quit, prescribing pharmacotherapy, and referring for behavioural support). Secondary outcomes were GPs' attitudes toward smoking cessation care, patients' intention to quit, and long-term quit rates. Outcomes were measured with GP self-report and patient report. Patients of trained GPs reported more often being asked about smoking behaviour compared with patients of untrained GPs (OR 1.94, 95% CI 1.45,2.60). According to GP self-report, the training increased the provision of quit-smoking advices (difference 0.56 advice per day, 95% CI 0.13,0.98) and the ability and intention of providing smoking cessation care. The authors found no effect on GPs' arrangement of follow-up, smokers' intention to quit, and long-term quit rates. After 1 hour of training, the study found significant differences between trained and untrained GPs on the frequency in which they asked about smoking (patient reported) and advised smokers to quit (GP self-reported). The training did not increase prescriptions of pharmacotherapy, referrals to behavioural support, or quit rates. Future training methods should focus on the GPs' ability, tools, and skills to arrange follow-up to ensure intensive smoking cessation support.[146, Level I]

Saito et al. (2012) evaluated a newly established practical training program to nurture pharmacists who can give smoking cessation instructions. The program was provided to 85 interns (45 males and 40 females) in Teikyo University Hospital. The one-day practical training was provided to groups comprised of five members each. The training consisted of studies on the adverse effects of smoking, general outlines of the outpatient smoking cessation service, experiencing Smokerlyzer, studies about smoking-cessation drugs, studies about a smoking cessation therapy using cognitive-behavioural therapy and motivational interviewing, and case studies applying role-playing. Before and after the practical training, the authors conducted a questionnaire survey consisting of The Kano Test for Social Nicotine Dependence (KTSND) and the assessment of the smoking status, changes in attitudes to smoking, and willingness and confidence to give smoking

cessation instructions. The overall KTSND score significantly dropped from 14.1 (SD 4.8) before the training to 8.9 (SD 4.8) after the training. The confidence to give smoking cessation instructions significantly increased from 3.4 (SD 1.9) to 6.2 (SD 1.3). Regarding the correlation between the smoking status and willingness and confidence to give smoking cessation instructions, the willingness and confidence were lower among the group of interns who either smoked or had smoked previously, suggesting that smoking had an adverse effect. A total of 88.2% of the interns answered that their attitudes to smoking had "changed slightly" or "changed" as a result of the training, indicating changes in their attitudes to smoking. Given the above, the authors concluded that the newly-established smoking cessation instruction training is a useful educational tool.[147,Level III]

Huber et al. (2012) assessed the effect on smoking cessation of training HIV care physicians in counselling in the Swiss HIV Cohort Study (SHCS), a multicentre prospective observational database. The intervention at the Zurich centre included a half day of standardized training for physicians in counselling and in the pharmacotherapy of smokers, and a physicians' checklist for semi-annual documentation of their counselling. Smoking status was then compared between participants at the Zurich centre and other institutions. The authors used marginal logistic regression models with exchangeable correlation structure and robust standard errors to estimate the odds of smoking cessation and relapse. Between April 2000 and December 2010, 11 056 SHCS participants had 121 238 semi-annual visits and 64 118 person-years of follow-up. The prevalence of smoking decreased from 60 to 43%. During the intervention at the Zurich centre from November 2007 to December 2009, 1689 participants in this centre had 6068 cohort visits. These participants were more likely to stop smoking (OR 1.23; 95% CI 1.07,1.42; p=0.004) and had fewer relapses (OR 0.75; 95% CI 0.61,0.92; p=0.007) than participants at other SHCS institutions. The effect of the intervention was stronger than the calendar time effect (OR 1.19 versus 1.04 per year, respectively). Middle-aged participants, injecting drug users, and participants with psychiatric problems or with higher alcohol consumption were less likely to stop smoking, whereas persons with a prior cardiovascular event were more likely to stop smoking. The authors concluded that an institution-wide training programme for HIV care physicians in smoking cessation counselling led to increased smoking cessation and fewer relapses in HIV patients.[148, Level II-3]

Schnoll et al. (2006) evaluated measures to increase physician adherence to smoking-cessation practice guidelines. A random sample of 2000 U.S. primary care physicians was ascertained from the American Medical Association (AMA) in 2002. Respondents (n = 1120, 62.3%) provided self-reported data about individual and practice characteristics and smoking-cessation practices. Data were analysed in 2005. Most primary care physicians (75%) advised cessation, 64% recommended nicotine patches, 67% recommended bupropion, 32% recommended nicotine gum, 10% referred to cessation experts, and 26% referred to cessation programs "often or always." Advising cessation was related to being older, having a faculty appointment, having trained staff for smoking counselling, and having confidence to counsel patients about smoking. Physicians who were internists, younger, and those with greater confidence to counsel patients about smoking recommended nicotine replacement more often. Prescribing bupropion was less common among older physicians, in the Northeast, with

trained staff available for counselling, and with a greater proportion of minority or Medicaid patients. Prescribing bupropion was more common among AMA-member physicians and physicians with greater confidence to counsel patients about smoking. Providing a referral to an outside expert or program was more common among female physicians, and physicians in the Northeast or West, with larger clinical practices, and with trained staff for cessation counselling. The authors concluded that current physician self-reported practices for smoking cessation suggest opportunity for improvement. Targeted efforts to educate and support subsets of primary care physicians may improve physician adherence and smoking outcomes.[149] Level III

Fore et al. (2014) examined the factors associated with nurses' perceived confidence in and importance of delivering cessation interventions to patients after receiving the Tobacco Tactics educational module, and whether self-reported delivery of smoking cessation services increased after the Tobacco Tactics educational programme was implemented. Two cross-sectional surveys among staff trained in the Tobacco Tactics programme, conducted at two months and 15 months post-training were conducted at Midwestern Veterans Affairs Medical Center. All staff members who attended the training were eligible to complete the surveys at two and 15 months post-training. Having a good understanding of the elements of smoking cessation interventions and satisfaction with training were associated with perceived confidence and importance of delivering smoking cessation interventions. Additionally, 86% of participants reported delivering cessation interventions 15 months post-training compared with 57% prior to training ($p < 0.0001$). The authors concluded that training nurses how to deliver tobacco cessation interventions increases delivery of cessation services and have the potential to increase quit rates and decrease morbidity and mortality among patient populations.[150,Level III]

7 DISCUSSION

The review included fair to high level of evidence consisting meta-analysis, systematic review, both randomised and non-randomised clinical trials involving young smokers through the elderly and attended either the primary care or hospital care setting, which assessed continuous abstinence (at least six months) with or without biochemical confirmation. However, reviews for other interventions, such as harm reduction and relapse prevention were not included.

In **general population**, pharmacotherapy consisting of varenicline, NRT, bupropion and non-pharmacological therapy including behavioural, psychological, technological based methods, quitlines, web- based methods were generally effective in reducing smoking among various types of population and disease conditions. Nicotine replacement therapy, bupropion, and varenicline were found to be consistently superior to placebo for smoking cessation and that none seemed to have an adverse event risk that would negate their use among the general adult population. There was however wide range of percentages of effectiveness which results in non-definitive conclusion found with the use of some non-pharmacological therapy and complementary and alternative methods of smoking cessation which can be attributable to differences in patient selection criteria, intervention intensity and outcome measures.

Nicotine replacement therapy, bupropion SR, and varenicline were not generally associated with an increased risk in serious adverse events among the general adult population, including major cardiovascular (CV) adverse events. Nicotine replacement therapy, however, was associated with a higher rate of any CV adverse event, although this was largely driven by low-risk events, typically tachycardia (a well-known risk). The reviews suggested a possible protective effect or very minor harm related to major CV events among users of bupropion SR, but these analyses were based on a small number of events.

Most of the strategies of combining agents available (e.g., two NRTs, a non-NRT, e.g. bupropion with a NRT) were found to be more efficacious especially for those smokers at highest risk of relapse, e.g. heavy smokers, smokers who have relapsed multiple times, or smokers with psychiatric co-morbidities. For example, combining the nicotine patch with a self - administered form of NRT (either the nicotine gum or nicotine inhaler) is more efficacious than a single form of nicotine replacement, and patients should be encouraged to use such combined treatments if they are unable to quit using a single type of first-line pharmacotherapy. Adverse effects and adherence to combination therapy were found similar to monotherapy and placebo.

The cumulative evidence also suggests that behavioural, pharmacologic, and combined medication and behavioural interventions for smoking cessation that are readily available to primary care patients and clinicians, can increase rates of smoking cessation in adults at six-month follow-up or longer. Multicomponent strategies were more effective when medications were used and a quit date was set. The combined intervention effects were significantly higher in participants from health care settings compared with community volunteers and tended to increase with greater numbers of sessions among interventions with an interpersonal component.

Researches on behavioural counseling interventions that include no pharmacologic treatments in adults represent a broad range of approaches. These interventions can range from in-person advice and support from physicians and nurses to a plethora of non-face-to-face formats (tailored and nontailored self-help materials, quitlines, outreach telephone counseling, mobile phone-based interventions, web-based interventions). Compared with various controls, behavioural interventions produced modest improvements in relative smoking cessation at six or more months. Physician advice, even brief, resulted in a significant relative improvement in quitting smoking compared with usual care. These data suggest that many options can effectively aid cessation and a range may provide options amenable to smokers' preferences. Nevertheless, given the small number of studies and heterogeneous findings, more research is needed on the use of non-tailored print materials, web-based and mobile phones interventions and in particular, using social media such as Whatsapp and Facebook to aid in cessation.

Among individuals with **mental health conditions**, there was no evidence on the effects of interventions on health outcomes among adults with mental health issues. The most common pharmacotherapy tested for patients with current or past depression was bupropion SR. Effects in individual trials were not statistically significant, with the exception of one trial in patients with past depression that included NRT as an adjunct in both study arms. There was

far more trial evidence available on the effectiveness of behavioural interventions among smokers with depression. There was evidence of a smoking abstinence benefit at six months among current or past smokers with depression with the addition of a mood management component to standard smoking interventions. Results in both populations had low statistical heterogeneity, moderate effect sizes, and adequate precision. However, trials on other types of behavioural interventions were lacking and high heterogeneity. There were no severe adverse events attributed to pharmacological smoking cessation interventions among people with depression or schizophrenia. There were no trials of behavioural interventions that suggested harm among those with mental illness.

In **pregnant women**, there was evidence of statistically significant infant health benefits from behavioural interventions. In terms of the effects of interventions on smoking cessation outcomes, there was considerably more evidence available on the effects of behavioural interventions during pregnancy than for pharmacotherapies. Although the most common type of intervention was counseling, trials of financial incentive interventions, feedback, social support, and health education had fairly consistent findings of benefit, including some significant individual trials. In contrast, there was no evidence of NRT efficacy for validated smoking cessation in late pregnancy based on the currently available evidence although all trials reported slightly more cessation events in the intervention group. In terms of harms related to cessation interventions, among pregnant women, there was no evidence of adverse events related to behavioural interventions among pregnant women. While evidence on the health outcomes of NRT is somewhat reassuring, there was limited power to rule out potential rare harms.

Limitations

This review has several limitations since it relied on the methods and quality of the included reviews and the limitations of the primary studies themselves. The comprehensiveness of this review is inevitably limited by the comprehensiveness and quality of the source reviews. It is presumed that each review generally included the full available and eligible evidence that data abstraction was accurate, and that analyses were scientifically sound. The authors did not reassess the risk of bias or quality of individual trials, instead we assessed the risk of bias that was presented in the review and interpreted results in light of these potential biases. Although most of the primary reviews that served as the basis for the main results included evidence through 2016, there may be evidence on particular population and intervention subsets that have been published since then. Most studies enrolled individuals who were all current smokers (or in some cases tobacco users or recent quitters) with varying degrees of baseline smoking (i.e., cigarettes smoked per day) and nicotine dependence. These trials took place within a very wide range of settings using different types of providers and included individuals with smoking-related disease and those with mental health conditions. In addition, they used some variant of techniques, for instance in conducting motivational interviewing among language-specific or culturally-specific population. Critical details in how it was modified for the particular study population, the training of therapists and the content of the counselling were sometimes lacking from trial reports. Most of the included studies within each review were conducted in the U.S, United Kingdom and

other parts of Europe which poses questions to the applicability of the results to the Malaysian population.

8 CONCLUSIONS

There was substantial fair to good level of retrievable evidence to suggest that quit smoking interventions comprising of pharmacotherapy (varenicline, NRT, bupropion), group behavioural support, phone counselling and text messaging were effective in reducing smoking rates in specific population and treatment settings. There was only limited fair level of retrievable evidence that suggest complementary and alternative methods and web-based methods were effective in promoting quit smoking.

Safety

There was substantial good level of retrievable evidence to suggest that quit smoking intervention especially pharmacological therapy was safe in reducing smoking rates among various populations. The side-effects were reported to be mild and tolerable.

Economic evaluation

There was substantial good level of retrievable evidence that found nation-wide quit smoking campaigns, pharmacotherapy, telephone counselling, stop smoking clinics, hospital initiated interventions were cost-effective when used in specific population in the world

Organizational issues

There was fair level of retrievable evidence that suggest quit smoking intervention to be feasible, acceptable and adaptable by patients as well as by the healthcare providers.

9 RECOMMENDATION

Based on the review, multicomponent interventions should be utilised to achieve greater long-term continuous smoking cessation. Treatment programme consisting of combination of behavioural and psychological strategies with pharmacotherapy (varenicline, bupropion SR and NRT) should be implemented.

More high quality research is needed on the effectiveness of nicotine vaccine, complementary and alternative therapy as well as on the direct comparisons between combinations and classes of drugs (such as cytisine versus varenicline or the use of combinations of pharmacotherapy and technological based therapy). In this era of technology, more high quality research is also needed on the different types of mobile telephone– and internet-based behavioural interventions for smoking cessation, including text messaging and smartphone applications, which have high potential applicability to the Malaysian population. Further research on the benefit and safety of cessation medications among pregnant women is warranted, including assessment of optimal dosage and treatment timing.

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Appendix 1

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 2

PTK-FM-02 Pin.1/2016

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL
QUIT SMOKING INTERVENTION

1.BACKGROUND INFORMATION

Smoking-related diseases such as cancer and cardiovascular disease are the main cause of premature death globally and in Malaysia particularly. Global estimates of about 6 million people worldwide die each year from causes attributed to smoking.[1] In Malaysia, it is estimated that one-fifth of disability adjusted life years (DALYs) and one-third of years of life lost (YLL) for Malaysians were due to smoking-related diseases.[2] Diseases related to smoking remained the top causes of death in Ministry of Health (MOH) hospitals, accounting for more than 15% of hospitalisations and 35% of in-hospital deaths.[2]

World Health Organization (WHO) reported an overall reduction in the prevalence of tobacco smoking among men in 125 (72%) countries and among women in 155 (87%) countries during the most recent decade (2000–10).[3] If these trends continue, there would be an estimated 1.1 billion current tobacco smokers in 2025.[3] According to the recent National Health and Morbidity Survey 2015, it was estimated that nearly five million Malaysians aged 15 years and above smoked.[4] The prevalence of current smoker was 22.8% with the highest percentage of smokers were among those aged 25 to 44 years. The proportion among males was reported to be 30 times higher compared to females (43.0%, 95% CI: 41.4, 44.6 vs 1.4%, 95% CI: 1.1, 1.8).[4] The prevalence of male smokers had reduced slightly from 43.9% in 2011 while the prevalence among females had increased from 1.0% in 2011. More than half (52.3%) of the current smokers had made an attempt to quit smoking in the last 12 months of the study with only less than 10% visited a healthcare provider.[4]

World Health Organization (WHO) aims to reduce the global burden of disease related to tobacco through WHO Framework Convention on Tobacco Control (FCTC) and the MPOWER package of tobacco policies.[5] Malaysia's targets according to WHO FCTC as well as the Global Non Communicable Diseases (NCD) targets, is to reduce our smoking prevalence down to 15% by the year 2025, and less than 5% by year 2045.[6]

The WHO MPOWER strategy focuses on six key activities which include monitoring tobacco use and prevention policies, protecting people from tobacco smoke, offering help to quit tobacco use, to warn about the dangers of tobacco, enforcing bans on tobacco advertising, promotion and sponsorship and raising taxes on tobacco.[7] In offering help to quit tobacco use, smoking cessation services can be offered at various levels ranging from healthcare and public health avenues to non-health channels including mass and social media.[7]These include physician-led and pharmacist-led interventions, practice nurse-led services, hospital-based patient discharge education, popular media campaigns, quitline telephone-based services and even social media networking with reported success in reducing smoking rates.[8-13]

Since their inception in 1999, the NHS Stop Smoking Services (SSS) in the United Kingdom (UK) has been providing services to smokers who would like to quit smoking. Services were established by primary care trusts (PCTs) and operated primarily in primary care settings delivering behavioural support and providing access to stop smoking medications. An observational study was conducted to evaluate the long-term outcomes for NHS Stop Smoking Services (ELONS study) and it was found to be effective in helping smokers to quit smoking.[14]Among 3000 smokers attending SSSs in nine areas of England, 41.2% and 8% of them were biochemically validated as abstinent from smoking at four weeks and one year follow-up, respectively.[14]Varenicline and combination NRT were both used frequently and

specialist one-to-one behavioural support were twice as likely to have remained abstinent than those who were seen by a general practitioner (GP) practice and pharmacy providers [odds ratio (OR) 2.3, 95% confidence interval (CI) 1.2, 4.6].[14] A meta-analysis conducted on 40 studies of randomised and quasi-randomised controlled trials found higher abstinence rates among those who received combination of pharmacotherapy and behavioural treatment compared to usual care or brief advice or less intensive behavioural support (RR 1.82, 95% CI 1.66, 2.00).[8] Another meta-analyses of five studies found that pharmacist-led interventions has higher abstinence rates in smokers compared with controls (RR 2.21, 95% CI 1.49, 3.29).[15]

In Malaysia, as of 31 December 2015, there were 486 quit-smoking clinics and 47 hospitals within the Ministry of Health facilities throughout the country that provide smoking cessation services including promotion, screening, counselling and pharmacotherapy services.[16] On average, around 15% to 17% of those who registered in these quit smoking clinics will eventually cease smoking. In line with the MPOWER strategy, the existing smoking cessation services in Malaysia needs to be strengthened and expanded to involve the private hospitals, clinics and the community pharmacies.[7]Activities of screening on smoking in schools are to be strengthened through the school dental team and counseling to stop smoking by the school counselors. To date, many tobacco control measures have been undertaken in concert with the anti-tobacco media approach to promote awareness among the public about the harmful effect of tobacco through the national anti-smoking media campaign known as the "*Tak Nak Merokok*" or Say No Campaign. This strategy could also be strengthened and to include stop smoking counselling through the phone line (Quit line). Therefore, a Health Technology Assessment (HTA) was requested by the Head of Tobacco Control Unit, Disease Control Division, Ministry of Health Malaysia to assess the effectiveness, safety and cost-effectiveness of various smoking cessation interventions in public and private sectors in increasing quit smoking rate.

2. POLICY QUESTION:

Which quit smoking interventions can be used in Malaysia to increase its quit smoking rate?

3. OBJECTIVES:

3.1 To determine the effectiveness of quit smoking interventions in increasing quit smoking rate

3.2 To determine the safety of quit smoking interventions

3.3 To determine the economic impacts of quit smoking interventions

3.4 To assess the ethical, legal, and organizational issues related to quit smoking interventions

Research questions

i. Which quit smoking interventions are effective in increasing quit smoking rate?

ii. Are quit smoking interventions safe?

iii. What are the economic impacts of quit smoking interventions in increasing quit smoking rate?

iv. What are the ethical, legal, and organizational issues related to quit smoking intervention in increasing quit smoking rate?

4. METHODS:

4.1 Search Strategy

Electronic database will be searched for published literatures pertaining to quit smoking interventions.

4.1.1 Databases as follows; MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and

FDA database.

4.1.2 Additional literatures will be identified from the references of the related articles.

4.1.3 General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.

4.1.4 There will be no limitation applied in the search such as year and language.

4.1.5 The search strategy will be included in the appendix.

4.2 Inclusion and exclusion criteria

4.2.1 Inclusion criteria

Population Problems	Smokers Tobacco and tobacco related product
Intervention	i. Pharmacological interventions ii. Nicotine Replacement Therapy e.g.nicotine gum, nicotine patch, nicotine nasal spray iii. Non-nicotine e.g. varenicline, bupropion iv. Behavioural intervention v. Traditional & Complementary Medicine – herbal (e.g. cytisine) vi. Laser treatment vii. Hypnosis viii. Web-based application ix. Mobile application x. Quitlines
Comparators	Current practice, no comparator
Outcomes	i. Effectiveness of quit smoking interventions e.g. • Prevalence of smokers • Quit rate/ Smoking cessation rate / Abstinence rate • Number of cigarettes smoked ii. Health related quality of life iii. Morbidity and mortality iv. Safety of quit smoking interventions (adverse events) v. Economic impacts 3. Cost-effectiveness 4. Cost-benefit vi. Medicolegal implication e.g. regulate accessibility to NRT vii. Social implication e.g. smoking related poverty viii. Organizational issues e.g training to ensure uniformity of programme
Study designs	HTA reports, systematic review with meta-analysis, systematic review, randomised controlled trial (RCT), cohort, case-control, cross-sectional and economic evaluation studies
Setting	Hospitals/Health Clinics/ General practitioners Dental clinics Community pharmacists Schools
English full text articles	

4.2.2 Exclusion criteria

i. Animal study
ii. Narrative review
iii. Experimental study
iv. Non English full text articles

Based on the above inclusion and exclusion criteria, study selection will be carried out

independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Critical Appraisal of Literature

The methodology quality of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP).

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted:

i. Details of methods and study population characteristics.
ii. Details of interventions and comparators.
iii. Details of individual outcomes for effectiveness, safety and cost associated with quit smoking interventions.

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion

4.4.2 Methods of data synthesis

Data on the effectiveness, safety and cost-effectiveness of quit smoking intervention will be presented in tabulated format with narrative summaries. No meta-analysis will be conducted for this Health Technology Assessment.

5. REPORT WRITING:

Appendix 3
Search strategy

Ovid MEDLINE(R) In -Process & Other Non -Indexed Citations and Ovid MEDLINE(R) 1946 to Present

1. Smoking/
2. ((reverse or tobacco or cigarette) adj smok*).tw.
3. smoking, tobacco.tw.
4. smoking, cigarette.tw.
5. smoking behavior*.tw.
6. smoker.tw.
7. Cigarette.tw.
8. tobacco.tw.
9. nicotiana tabacum.tw.
10. nicotine.tw.
11. nicotiana.tw.
12. tobacco,product*.tw.
13. cigar/
14. ((cigar or tobacco or cigarette or hookah or waterpipe or pipe) adj smoking).tw.
15. smoking,pipe.tw.
16. smoking, cigar.tw.
17. smoking,hookah.tw.
18. smoking,waterpipe.tw.
19. tobacco use*.tw.
20. tobacco usage.tw.
21. consumption, tobacco.tw.
22. tobacco consumption.tw.
23. tobacco dependence/
24. (tobacco adj (abuse or addiction or disorder*)).tw.
25. (nicotine adj2 (dependence or disorder*)).tw.
26. tobacco-use disorder.tw.
27. dependence, nicotine.tw.
28. dependence, tobacco.tw.
29. disorder, tobacco-use.tw.
30. snuff.tw.
31. plug pipe tobacco.tw.
32. smokeless tobacco/
33. tobacco, smokeless.tw.
34. smoking cessation/
35. (abstinence adj2 (smoking or tobacco)).tw.
36. (smoking adj (abstinence or dehabituation or stoping)).tw.
37. ((quit or stop*) adj smoking).tw.
38. (Tobacco adj2 cessation).tw.
39. nicotine replacement therapy.tw.
40. chewing gum*, nicotine.tw.
41. lozenge*, nicotine.tw.
42. nasal spray*, nicotine.tw.
43. (nicotine adj (chewing gum* or inhalant* or lozenge* or nasal spray* or patch* or polacril* or replacement product* or transdermal patch)).tw.
44. polacril*, nicotine.tw.
45. product*, nicotine replacement.tw.
46. transdermal patch, nicotine.tw.
47. Nicorette.tw.
48. patch, nicotine.tw.
49. Varenicline/
50. varenicline tartrate.tw.
51. varenicline.tw.
52. Champix.tw.
53. Chantix.tw.
54. Amfebutamone/

55. aplenzin.tw.
56. bupropion hydrochloride.tw.
57. bupropion.tw.
58. wellbutrin.tw.
59. (zyban adj (lp or sr * refill or sustained release)).tw.
60. zyntabac.tw.
61. budeprion.tw.
62. forfivo.tw.
63. odranal.tw.
64. quomen.tw.
65. Counselling/
66. Counsel*.tw.
67. traditional medicine/
68. (complementary adj (medicine or therapies)).tw.
69. alternative medicine/
70. (alternative adj (medicine or therapies)).tw.
71. cytisine.tw.
72. Tabex.tw.
73. ((polarity or spiritual) adj therap*).tw.
74. (therapeutic adj (cults or touch)).tw.
75. (behavior adj (modification* or therap*)).tw.
76. conditioning therap*.tw.
77. laughter therapy.tw.
78. medicine,alternative.tw.
79. mental healing.tw.
80. anthroposophy.tw.
81. orthomolecular medicine.tw.
82. reflexotherapy.tw.
83. laser treatment.tw.
84. psychotherapy.tw.
85. behavior therapy/
86. (behavior adj (training or treatment)).tw.
87. treatment behavior*.tw.
88. therap*, behaviour.tw.
89. web application/
90. Internet/
91. Blogging.tw.
92. world wide web.tw.
93. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
94. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 92
95. 93 and 94

Embase

1. Smoking/
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13. cigar/

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28. dependence, tobacco.tw.
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30. snuff.tw.
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32. smokeless tobacco/
33. tobacco, smokeless.tw.
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51. varenicline.tw.
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53. Chantix.tw.
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55. aplenzin.tw.
56. bupropion hydrochloride.tw.
57. bupropion.tw.
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61. budeprion.tw.
62. forfivo.tw.
63. odranal.tw.
64. quomen.tw.
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66. Counsel*.tw.
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68. (complementary adj (medicine or therapies)).tw.
69. alternative medicine/
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95. 93 and 94

EBM Reviews - Cochrane Database of Systematic Reviews

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33. tobacco, smokeless.tw.
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94. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 92
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(((((((Smoking[MeSH Terms]) OR cigar* AND smoking[Title/Abstract]) OR smoking[Title/Abstract] OR tobacco smoking[Title/Abstract] OR hookah smoking[Title/Abstract] OR waterpipe smoking[Title/Abstract] OR pipe smoking[Title/Abstract] OR Smoking Cessation[MeSH Terms] OR smoking cessation*[Title/Abstract] OR tobacco*[Title/Abstract] OR Tobacco Products[MeSH Terms] OR cigar*[Title/Abstract] OR tobacco product*[Title/Abstract] OR Tobacco Use[MeSH Terms] OR tobacco consumption[Title/Abstract] OR tobacco use[Title/Abstract] OR Tobacco Use Disorder[MeSH Terms] OR tobacco use disorder*[MeSH Terms] OR tobacco dependence*[Title/Abstract] OR nicotine use disorder*[Title/Abstract] OR nicotine dependence[Title/Abstract] OR Tobacco Smokeless[MeSH Terms] OR smokeless tobacco[Title/Abstract] OR Tobacco Use Cessation[MeSH Terms] OR smokeless tobacco cessation[Title/Abstract] OR tobacco cessation[Title/Abstract] OR tobacco use cessation[Title/Abstract])) AND (((Tobacco Use Cessation Products[MeSH Terms]) OR nicotine chewing gum*[Title/Abstract]) OR nicotine inhalant*[Title/Abstract]) OR nicotine lozenge*[Title/Abstract] OR nicotine nasal spray*[Title/Abstract] OR nicotine polacril*[Title/Abstract] OR nicotine replacement product*[Title/Abstract] OR smoking cessation product*[Title/Abstract] OR Nicorette[Title/Abstract] OR nicotine patch[Title/Abstract] OR nicotine transdermal patch[Title/Abstract] OR Varenicline[MeSH Terms] OR Champix[Title/Abstract] OR Chantix[Title/Abstract] OR varenicline tartrate[Title/Abstract] OR varenicline[Title/Abstract] OR bupropion[MeSH Terms] OR Amfebutamone.[Title/Abstract] OR bupropion hydrochloride[Title/Abstract] OR bupropion[Title/Abstract] OR esteve brand of bupropion hydrochloride[Title/Abstract] OR quomen[Title/Abstract] OR wellbutrin[Title/Abstract] OR zyntabac[Title/Abstract] OR Medicine Traditional[MeSH Terms] OR traditional medicine[Title/Abstract] OR Complementary Therapies[MeSH Terms] OR alternative medicine[Title/Abstract] OR alternative therapies[Title/Abstract] OR complementary medicine[Title/Abstract] OR complementary therapies[Title/Abstract] OR Behavior Therapy[MeSH Terms] OR behavior modification*[Title/Abstract] OR behavior therap*[Title/Abstract] OR conditioning therap*[Title/Abstract] OR smoking cessation*[Title/Abstract] OR Internet[MeSH Terms] OR internet*[Title/Abstract] OR user computer interface*[Title/Abstract] OR virtual system*[Title/Abstract] OR world wide web[Title/Abstract] OR Mobile Applications[MeSH Terms] OR mobile app*[Title/Abstract] OR mobile application*[Title/Abstract] OR portable electronic app*[Title/Abstract] OR portable software app*[Title/Abstract] OR Counseling[MeSH Terms] OR counsel*[Title/Abstract] OR Hotline[MeSH Terms] OR Hotline*[Title/Abstract] OR telephone hotline*[Title/Abstract]) AND "humans"[Filter] AND ((Clinical Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Controlled Clinical Trial[ptyp] OR Journal Article[ptyp] OR Meta-Analysis[ptyp] OR Pragmatic Clinical Trial[ptyp] OR systematic[sb]) AND ("2000/01/01"[PDat] : "2017/12/31"[PDat])

Appendix 4 ASSESSMENT OF RISK OF BIAS

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

Assessment of risk of bias of systematic review (CASP)

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Article 1	+	?	-	+

Assessment of risk of bias of RCT (Cochrane)

Criteria assessed	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Article 1	+	?	-	+	?	-

Assessment of risk of bias of cohort (CASP)

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Article 1	+	?	-	+	?

Assessment of risk of bias of case-control (CASP)

Criteria assessed	Selection cases and control	Exposure accurately measured	Confounding factors
Article 1	-	+	?

Assessment of risk of bias of economic evaluation (CASP)

Criteria assessed

A well-define question posed?	+	+	+	+
Comprehensive description of competing alternative given?	?	?	?	?
Effectiveness established?	-	-	-	-
Effects of intervention identified, measured and valued appropriately?	+	+	+	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	?	?	?	?
Costs and consequences adjusted for different times at which they occurred (discounting)?	-	-	-	-
Results of the evaluation?	+	+	+	+
Incremental analysis of the consequences and costs of alternatives performed?	?	?	?	?
Sensitivity analysis performed?	-	-	-	-

Assessment of risk of bias of quasi experimental studies (non-RCT) (JBI)

Criteria assessed

Clear what is the cause and what is the effect?	+	+	+	+
Participants included in any comparisons similar?	?	?	?	?
Participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	-	-	-	-
Was there a control group?	+	+	+	+
Multiple measurements of outcome pre and post the intervention/ exposure?	?	?	?	?
Follow-up complete, and if not was follow-up adequately reported and strategies to deal with the loss to follow-up employed?	-	-	-	-
Outcomes of participants included in any comparisons measured in the same way?	+	+	+	+
Outcome measure in reliable way?	?	?	?	?
Appropriate statistical analysis used?	-	-	-	-

Assessment of risk of bias of pre-post studies with no control (NIH)

Criteria assessed

Question or objective clearly stated?	+	+	+	+
Eligibility/selection criteria for study population clearly described?	?	?	?	?
Were participants representative for those who would be eligible for the test/ service/ intervention in the population of interest?	-	-	-	-
Were all eligible participants that met the prespecified entry criteria enrolled?	+	+	+	+
Sample size sufficiently large to provide confidence in findings?	?	?	?	?
Test/service/intervention clearly described and delivered consistently?	-	-	-	-
Outcome measures prespecified, valid, reliable, and assessed consistently?	+	+	+	+
People assessing the outcome measures blinded to participants exposure/ interventions?	?	?	?	?
Loss to follow-up after baseline 20% or less? Loss to follow-up accounted for in the analysis?	-	-	-	-
Statistical methods examine changes in outcome measures from before to after intervention? p value?	+	+	+	+
Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?	?	?	?	?
If intervention conducted at group level, did statistical analysis take into account of individual level data to determine effects at group level?	-	-	-	-

Appendix 5

Evidence table can be downloaded from:

- MOH website : http://www.moh.gov.my/index.php/pages/view/1692
- MaHTAS apps : HTA: Quit Smoking Interventions

Appendix 6

LIST OF EXCLUDED STUDIES

1. Bernstein SL, D'Onofrio G, Rosner J et al. Successful Tobacco Dependence Treatment in Low-Income Emergency Department Patients: A Randomized Trial. Ann Emerg Med. United States; 2015;66(2):140–7.
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