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TOBACCO CESSATION GUIDELINES FOR HIGH-RISK POPULATIONS

ATHENS 2017

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FOREWORD

SMOKING IS A DISEASE. It is the biggest epidemic of all time. To tackle the problem, the Global Community has created the Framework Convention on Tobacco Control (FCTC), the largest global Treaty of WHO. In addition, the European Union has adopted two clear and strict directives regulating tobacco products licensing and use (Tobacco Products Directives I and II).

However, the solution to the problem remains challenging as we confront a severe addiction. Nicotine, the main ingredient of tobacco products, is considered to be the third most addictive substance after heroin and cocaine. Complex and not fully elucidated destructive neurobiological and behavioral mechanisms compose the personality of the typical addicted smoker who desires but fails to quit.

The medical practice of smoking cessation requires specialized knowledge. Almost all organizations dealing with tobacco control have issued relevant guidelines. Quite distinctively, the European Network for Smoking and Tobacco Prevention has issued first and second editions of a general cessation guideline readily available in many European languages.

Generalization and simplicity are imperative for success in preventive medicine. However, medical science of the twenty-first century is systematically moving toward more individualized therapeutic approaches. In other words, "One key cannot open all doors". The "TOB.g project" and ultimately this book represent the first innovative action towards the scientific application of this principle in tobacco cessation.

Aim of the project is to provide an individualized approach to smoking cessation within five clearly distinctive subpopulations of smokers, who obviously cannot continue to be treated as a single entity. Teenagers, cardiovascular patients, pregnant women, patients with diabetes or chronic obstructive pulmonary disease belong to clearly distinct groups and reasonably require a tailored approach to treatment.

The course to successful cessation is a long and arduous one. This book represents the first step toward a new consideration, a new direction and a new path, leading to a more efficient approach to a major Public Health concern.

The entire project has evolved from the general scopes of the ENSP and in accordance with Article 14 of the FCTC.

Panagiotis K. Behrakis, MD, PhD, FCCP

SMOKING CESSATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

SMOKING CESSATION IN PATIENTS WITH CARDIOVASCULAR DISEASE

1.

SMOKING CESSATION DURING PREGNANCY AND THE POSTPARTUM PERIOD

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About this Guideline

This special chapter of the European Tobacco Treatment Guideline is intended to summarize evidence regarding the health risk associated with tobacco use and second-hand smoke exposure during pregnancy and the postpartum period as well as effective approaches to supporting cessation and preventing relapse.

Within the chapter clinical practice recommendations are presented for health care professionals working with woman during the pre-natal and postpartum periods. The GRADE evidence grading system has been used to rate the quality of evidence supporting each recommendation. GRADE uses 4 evidence grading categories: 'high', 'moderate', 'low', 'very low' (see table below). The evidence grading scale reflects the type, quality and quantity of available evidence supporting the guideline recommendation. The level of evidence grading appears in brackets at the end of each recommendation statement.

GRADE - Evidence Grading Categories:

CODE	QUALITY OF EVIDENCE	DEFINITION
A	High	– Further research is very unlikely to change our confidence in the estimate of effect. – Several high-quality studies with consistent results. – In special cases: one large, high-quality multi-center trial
B	Moderate	– Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. – One high-quality study. – Several studies with some limitations.
C	Low	– Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. – One or more studies with severe limitations.
D	Very Low	– Any estimate of effect is very uncertain. – Expert opinion. – No direct research evidence. – One or more studies with very severe limitations.

EXECUTIVE SUMMARY

SMOKING CESSATION DURING PREGNANCY AND THE POSTPARTUM PERIOD

Health Effects of Smoking in Pregnancy

Maternal tobacco use and exposure to second-hand smoke during pregnancy imposes a significant risk to the unborn foetus and new born. Maternal smoking has been associated with a number of adverse pregnancy outcomes.[1] Tobacco use during pregnancy is in fact the most preventable cause of adverse pregnancy outcomes. Perinatal mortality rates are 150 per cent greater when the mother is a smoker, and smoking is estimated to be responsible for 15 per cent of all cases of premature birth.[1-3]

The adverse effects of tobacco use and second-hand smoke exposure have also been shown to extend into childhood and are associated with increased risk of congenital malformation, sudden infant death syndrome, genetic-related hereditary diseases, perinatal mortality and morbidity, short stature, cognitive delays, and neurologic disorders.[4-10] Exhibit 1 presents a summary of the known health effects of tobacco use during pregnancy.

EXHIBIT 1:
Health effects of maternal smoking on the foetus, new born, and children

IMPACT PERIOD	HEALTH EFFECT
Antenatal Impact	– Placental abnormalities – Ectopic pregnancy – Placental detachment – Placenta praevia – Pre-eclampsia – Still birth – Spontaneous miscarriage – Premature rupture of membranes
Impact Postnatal	– Increased perinatal mortality – Premature birth (twice as great) – Intra-uterine growth retardation – Low birth weight infant 150-250 grams smaller – Sudden Infant Death Syndrome (SIDS) – Birth Defects
Impact in child's later life	– Type 2 Diabetes – Obesity – Hypertension – Reduced High Density Lipoprotein cholesterol – Increased hospitalization – Bronchial asthma, lower respiratory infection, decreased lung function – Conduct disorder, Attention Deficit Disorder and hyperactivity – Impaired academic performance – Significant increase in psychiatric disorders

Second-hand Smoke Exposure

Second-hand smoke (SHS) exposure during pregnancy is associated with multiple health risks to the unborn foetus. This includes a significantly increased risk of preterm birth, broncho-pulmonary dysplasia, congenital malformation, and wheezing/asthma etc.[6, 11-13] Specifically, pregnant women who are exposed to SHS are 23% more likely to experience stillbirth and 13% more likely give birth to a child with a congenital malformation.[14, 15]

100% smoke-free environments should be a priority during pregnancy for all women, including non-smokers. Smoke-free environments should be maintained during the post-natal period for new borns and children.

Tobacco Use in Pregnancy

Despite the magnitude of the risks associated with tobacco use during pregnancy, an estimated 6-19% of woman in Europe will continue to smoke during pregnancy and a large portion of woman who quit will return to smoking following pregnancy.[16] Quitting smoking can be extremely difficult and few recognize that due to both physiological and other factors that it can be even more difficult for pregnant woman to quit smoking. For example rates of nicotine metabolism during pregnancy increase 60-140% and contributing to greater nicotine withdrawal and difficulty with quitting.[17]

Pregnant smokers fall into three groups:

- Those who quit spontaneously when they found out they were pregnant.
- Those who cut back on smoking when they found out they were pregnant.
- Those who continue to smoke during pregnancy.

Smoking Cessation Interventions in Pregnancy

There is no safe level of smoking in pregnancy and women should be advised to quit smoking completely. More specifically, it was found that the relative risk of ectopic pregnancy increased to 1.6 times that of non-smoking women for those who smoked from 1-5 cigarettes daily, and to 2.3 times for women who smoked 11-20 cigarettes daily.[18] The greatest gain in health benefits comes from full cessation during pregnancy rather than reducing smoking.[19, 20] Furthermore, women should be encouraged to quit smoking before becoming pregnant to ensure optimal pregnancy outcomes. Importantly, serious adverse effects of smoking are reversible if smoking is stopped early in pregnancy. Evidence has shown that women who quit smoking during the first trimester of pregnancy give birth to infants of similar weight to those that never smoked.[21, 22]

Increased concern of expectant parents about the risks of smoking on pregnancy outcomes and the health of their new born creates a "teachable moment" where expectant mother's may have increased receptivity to quitting smoking.[23] The same is true for expectant fathers and other members of the family.

Health professionals have an important role to play in supporting cessation among pregnant women as well as other members of the family. Given the significant health risks imposed to the unborn foetus and new borns as a result of tobacco use, it is critical for health professionals working with pregnant woman, including family physicians, midwives, obstetricians and gynaecologist, and nurses, be familiar with the latest evidence and be comfortable intervening and supporting women with achieving cessation.

The "5 As" (Ask, Advise, Assess, Assist, Arrange) can be used as a clinical model for supporting cessation among pregnant woman (See Exhibit 2). As part of the 5 As model, all pregnant women should have both their smoking status and second-hand smoke exposure assessed as part of routine examinations. Pregnant woman often do not disclose their smoking status, likely due to the social stigma of tobacco use during pregnancy. Honest disclosure of smoking status can be increased by as much as 40% by using multiple-choice questions instead of a simple yes/no question.[24-26] Validation of tobacco use exposure with carbon monoxide testing is recommended. Non-judgmental advice to quit and support with quitting should be pro-actively offered to pregnant woman and providers should arrange follow-up with patients.[24-26]

Counselling Interventions

Intensive counselling is often required to support cessation among pregnant women who are unable to quit on their own. Intensive counselling has been shown to significantly increase smoking cessation among pregnant woman compared with usual care (30 studies; average risk ratio (RR) 1.44, 95% confidence interval (CI) 1.19 to 1.73).[27] In most studies an intensive intervention lasting more than 15 minutes was found to be more effective than the shorter and less individualized interventions (18 studies; average RR 1.25, 95% CI 1.07 to 1.47). Referral to specialized smoking cessation services, when available, is recommended.

Internet-based interventions, financial incentives, or interventions involving the spouse or peers are promising intervention strategies being explored to support cessation among pregnant smokers however, more research is required to better understand their value.

Quit Smoking Medications

While nicotine replacement therapy (NRT) is considered a first-line quit smoking therapy in adult populations, the use of NRT during pregnancy has been an area of controversy in international clinical practice guidelines. A 2015 Cochrane review found no evidence that the use of NRT for smoking cessation in pregnancy had either a

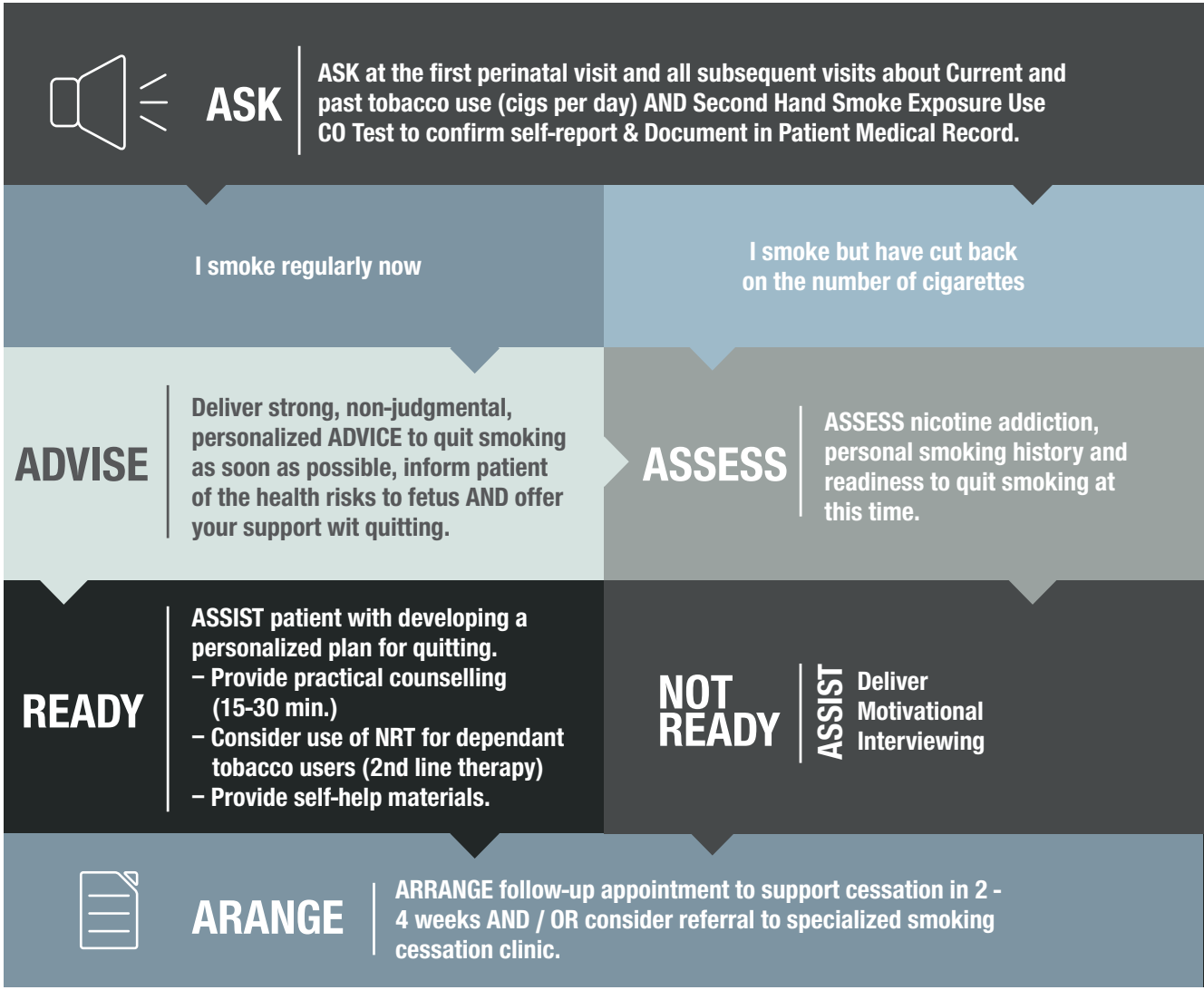
beneficial or harmful effect on birth outcomes.[28] This review however also did not find evidence to support increased rates of cessation among pregnant women who used NRT for smoking cessation compared to controls.[28] Poor compliance with NRT treatment is commonly reported among those studies conducted to date and limits our ability to accurately understand the efficacy of NRT among pregnant women. Despite limitations of the evidence, the potential risk from the use of NRT is considered magnitudes less than continued tobacco use and as such the risk benefits of using NRT should be discussed with woman who are unable to quit on their own. Given the lack of efficacy data, NRT should be considered a second-line therapy. Adequate dosing and duration of NRT is likely to improve outcomes.

The use of varenicline or bupropion is not recommended during pregnancy due to a lack of research regarding safety and efficacy.[28]

Post-Partum Relapse Rates

Postpartum relapse rates are extremely high (29-85%) among women who are successful with quitting during pregnancy. Many woman who quit smoking during pregnancy, do so with the intention of resuming smoking after birth. Stress, post-natal depression, concerns about weight gain and having a smoking partner, lower socio-economic status are also known to be contribute to relapse. Supporting maintenance of cessation following pregnancy is an important secondary target for intervention.[29, 30] It is recommended that clinicians address plans for continued cessation following pregnancy early in the quitting process and that counselling support extend into the postpartum period.

EXHIBIT 2: 5 AS TOBACCO TREATMENT PROTOCOL



PREGNANT & POSTPARTUM WOMAN

ADVISE all woman and partners to ensure 100% smoke free environment at home, and other settings (restaurants, social gatherings).

ADVISE

I stopped when I found out I was pregnant

I stopped before I found out I was pregnant

I have never smoked

ADVISE

Congratulate on success with quitting & reinforce importance of styaing quit throughout the pregnancy and the postpartum period.

ASSESS intentions for remaining smoke free postpartum.

ASSESS

ASSIST

- Provide behavioural counselling to support cessation during post-pardum period.
- Assess smoking status and intentions regurarly.

Summary of Key Recommendations for Health Professionals:

- There is no safe level of smoking in pregnancy and women should be advised to quit smoking completely (Level of Evidence A).
- Pregnant women should quit smoking as early as possible during the first trimester of pregnancy and stay smoke-free after birth (Level of Evidence A).
- Health professionals should inform expectant parents about the health risks of second-hand as well as third-hand smoke to the mother, foetus, and new born (Level of Evidence D).
- Health professionals should advise pregnant women to maintain 100% smoke-free environments by banning smoking in their homes and cars and avoiding settings in which there may be exposure to second-hand smoke (Level of Evidence A).
- All health professionals working with pregnant women including family physicians, midwives, obstetricians and gynecologist, and nurses should be familiar with the latest evidence and be comfortable intervening and supporting women with achieving cessation (Level of Evidence A).
- The "5 As" (Ask, Advise, Assess, Assist, Arrange) can be used as a clinical model for supporting cessation among pregnant women (Level of Evidence B).
- All pregnant women should have both their smoking status and second-hand smoke exposure assessed as part of routine examinations (Level of Evidence A).
- Health professionals should deliver strong non-judgmental advice to quit to all women who smoke and assist tobacco users with cessation, which includes follow-up throughout the duration of the pregnancy and early postpartum period (Level of Evidence A).
- Women unable to quit smoking should receive intensive counselling and support with quitting as early as possible in their pregnancy (Level of Evidence A).
- Counselling interventions are effective in increasing quit rates and significantly reducing low birth weight, increasing mean birth weight, and reducing neonatal intensive care admissions (Level of Evidence A).
- When available women unable to quit should be referred to specialized cessation support. Health professionals should follow-up to ensure treatment is undertaken (Level of Evidence A).
- The use of nicotine replacement therapy (NRT) is preferred to continued smoking during pregnancy. Evidence in terms of its effectiveness among pregnant women is however mixed. As such, NRT can be considered a second-line therapy for pregnant women who are unable to for quit with counselling support alone (Level of Evidence B).
- Due to a lack of research bupropion and varenicline are not recommended for smoking cessation during pregnancy (Level of Evidence – n/a).
- Parents should be encouraged to remain smoke-free in the postpartum period. A pregnant woman's social

support network, including her spouse and close family should be involved in supporting smoke-free environments in spaces shared by the new born (Level of Evidence D).
- Postpartum care should address relapse prevention for both parents before hospital discharge and during post-natal home visits (Level of Evidence A).
- Parents, who continue to smoke at the time their babies are admitted to neonatal intensive care units (NCIU), should be referred to local smoking cessation programs (Level of Evidence C).

1.0
TOBACCO USE AND CESSATION IN PREGNANCY

1.1 Prevalence of tobacco use during pregnancy

Addressing tobacco use and second-hand smoke (SHS) exposure during pregnancy is a significant public health priority.[13]

A large proportion of women will stop smoking during pregnancy. Data suggest that up to 49% of women who smoked before pregnancy 'spontaneously quit' before their first antenatal visit.[27, 31, 32] The perceptions of pregnant smokers regarding the health risks of personal tobacco use and exposure to passive smoking have been identified as important factors influencing their decision to quit.[15, 33]

According to the European Perinatal Health Report on smoking during pregnancy in Europe, in most countries more than 10% of pregnant women continue to smoke during pregnancy (See **Table 1**).[7, 16] The prevalence of smoking during pregnancy varies from country to country. European countries with the highest proportion of tobacco users during pregnancy are: France (17.7%), Scotland (19%), Wales (16%), Northern Ireland (15%) and Spain (Catalonia – 14.4%).[16]

A second study involving 15 European countries (n=8,344) in 2011/12 found 35.3% of woman smoked before pregnancy.[34] This study found 26.2% of women continued smoking during pregnancy with 11.4% of report-

ed smoking more than ten cigarettes per day. This study also documented a large variation among the 15 European countries in prevalence of tobacco use.[34]

Specific sub-groups of women are more likely to continue to use tobacco during pregnancy. Single women, teenagers and those in the lowest socio-economic brackets, and suffering from depression or other mental health illnesses are more likely to smoke during pregnancy.[35] An estimated 50% of individuals who smoke during pregnancy have a mental health illness.[36]

1.2 Postpartum relapse rates

During the first 12 months of the postpartum period there is a very high risk of relapse to smoking by women who stopped during pregnancy or an increase in the number of cigarettes smoked by those who reduced smoking significantly during pregnancy.[37] Data suggests that between 29% and 85% of women who quit smoking relapse postpartum.[29, 30]

The specific events, factors, or decisions that precipitate a woman's resolution to quit are not necessarily the same as those that trigger a woman to smoke again.[30] Among woman who quit smoking during pregnancy who received intervention for smoking cessation, between 6.2% and 37.2% remained smoke-free.[30] Importantly, there is an association between tobacco use and decisions related to breastfeeding. Mothers who smoke tobacco after delivery are more than twice as likely not to be breastfeeding postpartum.[38-40] The value of breastfeeding for all infants, especially for premature infants, has been well established.[41, 42] As such, supporting a mother's efforts to remain smoke-free during postpartum period may be an important factor to prolong the duration of breastfeeding.

TABLE 1:
Percentage of women who report tobacco use during pregnancy in Europe and internationally

		DEFINITION OF PERIOD		PERIOD 1			PERIOD 2		
Country/ coverage	Source	Period 1	Period 2	All stated N	Not stated N	Smokers %	All stated N	Not stated N	Smokers %
Belgium									
Czech Republic	1		During				114407	0	6.2
Denmark	1		During				60947	1256	12.8
Germany	1		During				625615	0	8.5
Estonia	1	1st Trim	During	15111	535	9.1	15111	535	7.8
Ireland									
Greece									
Spain									
ES: Catalonia	7	Before	3rd Trim	NA	NA	26.7	NA	NA	14.4
ES: Valencia	6	1st Trim		4629	53	15.8			
France	1	Before	3rd Trim	13933	748	30.6	14087	594	17.1
Italy									
Cyprus	1	1st Trim		8312	43	11.5			
Latvia	1			19003	0	10.4			
Lithuania	1	Before	During	30568	0	7.0	30568	0	4.5
Luxembourg	1		3rd Trim				6370	70	12.5
Hungary									
Malta	1	1st Trim		3952	0	8.2			
Netherlands	4	1st Trim	>1st Trim	1441	7	10.5	1441	7	6.2
Austria									

	DEFINITION OF PERIOD			PERIOD 1			PERIOD 2		
Country/ coverage	Source	Period 1	Period 2	All stated N	Not stated N	Smokers %	All stated N	Not stated N	Smokers %
Poland	3	Before	3rd Trim	2765	128	24.6	2697	196	12.3
Portugal									
Romania									
Slovenia	1	1st Trim		22000	0	11.0			
Slovakia									
Finland	1	1st Trim	>1st Trim	59120	1301	15.5	59.120	1301	10.0
Sweden	1	1st Trim	3rd Trim	110212	3276	6.5	108843	4645	4.9
United Kingdom	1	Before or during	During	15315	NA	26.0	15315	0	12.0
UK: England	1	Before or during	During	7139	NA	26.0	7139	0	12.0
UK: Wales	1	Before or during	During	2571	NA	33.0	2571	0	16.0
UK: Scotland	12		During				53087	3442	19.0
UK: Northern Ireland	1	Before or during	During	2592	NA	28	2592	0	15.0
Iceland									
Norway	1	1st Trim	3rd Trim	52501	9038	18.6	51100	10439	7.6
Switzerland									

Source: Euro-Peristat project with SCPE and EUROCAT. European Perinatal Health Report. The health and care of pregnant women and babies in 2010. May 2013. Available www.europeristat.com [13]

2.0
HEALTH EFFECTS OF SMOKING DURING PREGNANCY AND POSTPARTUM PERIOD

2.1 The health effects of smoking on the foetus

When a pregnant woman smokes, the foetus inherently becomes a passive smoker. Tobacco use in pregnancy has significant and well established, adverse effects on the health and growth of the foetus.[1, 43] **Table 2** presents a summary of the known risk of tobacco use during pregnancy to the foetus and new born. Importantly, perinatal mortality rates are 150% greater when the mother is a smoker,[2] and data suggest that smoking is responsible for 15% of all cases of premature birth.[3] A meta-analysis of eight studies indicated that abruption placentae is greatly increased among pregnant smokers with an odds ratio (OR) of 1.62 [95% CI 0.46 to 1.77] compared to non-smokers.44 Smoking was also found to be one of the most important causes of premature rupture of membranes (PRM), with an OR of 1.81 [95% CI 1.36 to 2.26] based on pooled data for six studies.[44]

According to a US cohort study, which was based on the data from medical records of births, there is a dose-related association between the number of cigarettes smoked on a daily basis and the occurrence of placenta praevia; the increase in relative risk for placenta praevia associated with smoking was 4.4% for singleton births and 2.7% for twin births.[45]

Research has shown that perinatal mortality is increased among the offspring of pregnant smokers regardless of the number of cigarettes daily smoked.[20, 46-49] More specifically, it was found that the relative risk of ectopic pregnancy increased to 1.6 times that of non-smoking women for those who smoked from 1-5 cigarettes daily, and to 2.3 times for women who smoked 11-20 cigarettes daily.[18] The greatest gain in health benefits comes from full cessation during pregnancy rather than reducing smoking.[47, 50]

2.2 The effects of maternal smoking on the health of infants and children

Tobacco smoking during pregnancy is associated with significantly increased risk of intrauterine growth retardation, preterm birth, low birth weight, miscarriage, stillbirth, congenital malformation, sudden infant death

syndrome, genetic-related hereditary diseases, perinatal mortality and morbidity, short stature, cognitive delays, and neurologic disorders.[4-7, 9, 10, 51] Exposure of the foetus to maternal smoking may also effect fetal birth weight, fetal growth such as height, head perimeter, perimeter of thorax and shoulders and affect the growth of the lungs and brain, with possible effects that could continue into later life.[52-55] Active maternal smoking during pregnancy can also effect the development of other diseases in infancy such as Sudden Infant Death Syndrome (SIDS),[56,57] infant respiratory function[58-60] and the development of asthma in childhood.[61] Maternal smoking is also an important risk factor associated with the incidence of asthmatic bronchitis during the first year of life.[62]

Multiple epidemiologic studies argue that exposure to cigarette smoke during pregnancy can affect the fetal nervous system and could lead to behavioural disturbance in the infant, the child, or even the young adult. 63,64 Tobacco use during pregnancy is associated with the development of attention deficit disorders in children 65 and a higher risk of hyperactivity with more specific learning difficulties 66 and distractibility.[67] Even though the relative risk of autism occurrence is low at a rate of around 1/1,000 births,[68] an association with maternal daily smoking in early pregnancy has been documented in national observational study in Sweden.[69]

TABLE 2: Health effects of maternal smoking on the fertility, foetus, new born, and children

IMPACT PERIOD	HEALTH EFFECT
Fertility	Delayed conception (average 2 months)
	Infertility females (60% increase)
	Infertility males
	Reduced odds of conception with reproductive assistance
Antenatal Impact	Placental abnormalities
	Ectopic pregnancy (OR 2.5)
	Placental detachment
	Placenta praevia (OR 2.1)
	Pre-eclampsia (OR 0.51)
	Still birth (OR 1.1-3.2)
	Spontaneous miscarriage (OR 1.8)
	Premature rupture of membranes (OR 1.8)

IMPACT PERIOD	HEALTH EFFECT
Impact Postnatal	Increased perinatal mortality (150%)
	Premature birth (twice as great)
	Intra-uterine growth retardation
	Low birth weight infant 150-250 grams smaller
	Sudden Infant Death Syndrome (SIDS), OR 2.25
	Birth Defects
Impact in child's later life	Type 2 Diabetes (OR 1.1)
	Obesity (OR 1.52)
	Hypertension (1.5-5.4 mm HG increase)
	Reduced High Density Lipoprotein cholesterol (0.014 mmol/L decrease)
	Increased hospitalization
	Bronchial asthma, lower respiratory infection, decreased lung function
	Conduct disorder, Attention Deficit Disorder and hyperactivity
	Impaired academic performance
	Significant increase in psychiatric disorders

Maternal smoking during pregnancy can influence the future fertility of male infants.[70] Data found, the more the mother smokes during pregnancy, the greater the adverse effect in the reduction of volume and concentration of sperm.[70]

Additionally various studies have claimed that when the mother smokes during pregnancy, the occurrence rate of congenital abnormalities increases, particularly the occurrence of cleft palate and cleft lip.[71] According to an observational study of 1,974 children by Wisborg et al., investigated the relationship between smoking during pregnancy and the hospitalization of infants younger than 8 months, and found that children of mothers who smoked[15] or more cigarettes daily had twice the risk of hospitalization than those whose mothers had never smoked.[72] According to the findings of a population-based retrospective cohort study conducted in the State

of Ohio USA, which used birth records from 2006 to 2012, smoking of any duration in pregnancy is associated with increased Fetal Growth Restriction Risk.[73]

RECOMMENDATIONS:

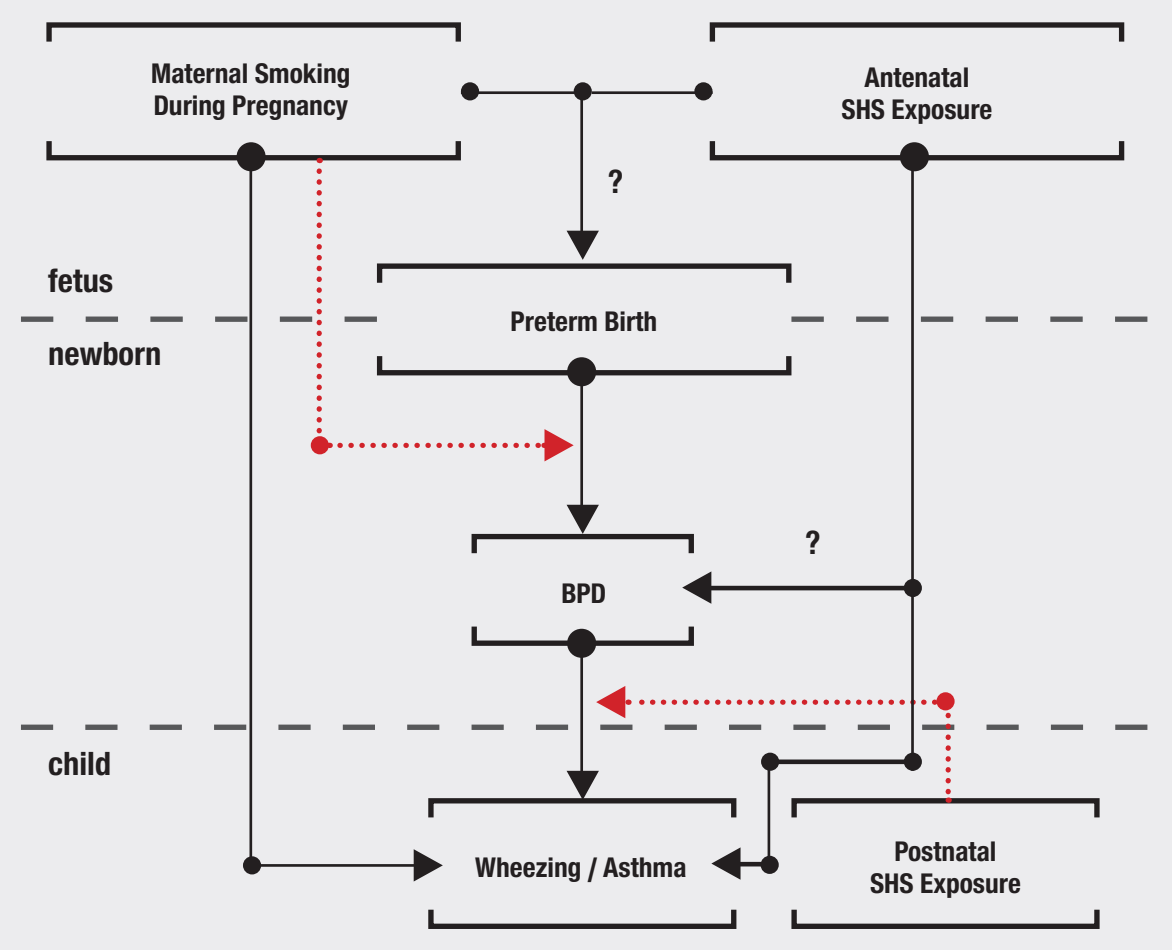
- There is no safe level of smoking in pregnancy and women should be advised to quit smoking completely (Level of Evidence A).

2.3 Second-hand smoke exposure

Second-hand smoke (SHS) exposure can affect the health of mother and foetus of both smoking and non-smoking women.[7, 13] SHS exposure during pregnancy is associated with multiple health concerns in the perinatal period (**Figure 1**) including an increased risk of preterm birth, bronchopulmonary dysplasia, congenital malformations, and wheezing/asthma etc.[6, 11-13] Pregnant women who are exposed to SHS are 23% more likely to experience stillbirth and 13% more likely give birth to a child with a congenital malformations.[15, 56]

Among non-smoking women and women who manage to quit smoking or cut down the amount of smoking in pregnancy, exposure to SHS from their partners and other family members, or social environments is common in many EU countries.[4, 12,74] The two most prominent factors affecting the exposure of women to passive smoking is dining at restaurants and having a partner who smoked. Maintaining a smoke-free environment should be a priority for all parents.[11]

FIGURE 1: Impact of tobacco smoke exposure on preterm birth and its respiratory complications



Source: Wagijo, et al. (2015) Reducing tobacco smoking and smoke exposure to prevent preterm birth and its complications. Paediatr. Respir. Rev., http://dx.doi.org/10.1016/j.prrv.2015.09.00213

2.4 Third-hand smoke exposure

Third-hand smoke (THS) has been more recently brought to the forefront and has particular implications during pregnancy and the postpartum period. THS is the residual tobacco smoke pollutants that remain on surfaces and in dust after tobacco has been smoked.[179] Studies show that THS clings to hair, skin, clothes, furniture, drapes, walls, bedding, carpets, dust, vehicles and other surfaces, even long after smoking has stopped and is resistant to normal cleaning.[179] It is understood that THS reacts with oxidants and other compounds to yield secondary pollutants.[75] Research has found that THS contains cancer-causing substances, posing a potential health hazard to non-smokers who are exposed to it. However, human exposure to THS has not yet been thoroughly studied.[179,180] Multiple groups are presently studying the health risks to humans of THS in order to fill this evidence gap. THS is particularly relevant to health of infants and children who typically spend more time indoors and have age-specific behaviours that may increase their exposure to the potential health hazards of THS.[179,180] Presently there is very little awareness among the general public about the health risks of THS and its danger to human health.[180]

RECOMMENDATIONS:

- Parents should be informed about the health risks of second-hand as well as third-hand smoke to the mother, foetus, and new-born (Level of Evidence D).
- Health professionals should advise pregnant women to maintain 100% smoke-free environments by banning smoking in their homes and cars and avoiding settings in which there may be exposure to second-hand smoke (Level of Evidence A).

2.5 Health Benefits of Smoking Cessation during Pregnancy

There is good evidence that stopping smoking as early as possible during pregnancy can reduce health risks.[76,77] Women who quit smoking prior to the first 3-4 months of pregnancy, give birth to infants of similar weight to those that never smoked.[21, 22] McCowan et al. (2009) in a prospective cohort study indicated that the serious adverse effects of smoking may be reversible if smoking cessation occurs early in pregnancy.[78] Among women who quit smoking before 15 weeks of gestation, the rate of spontaneous preterm birth and small for gestational age infants did not differ from non-smokers.[78] A large Finnish population-based cohort study of 1,164,953 singleton pregnancies from 1991 to 2010 found that quitting smoking in the first trimester of pregnancy reduces obstetric risks like prematurity, stillbirth, low birth weight and small for gestational age newborns at levels close to those of non-smokers.[79] But the use of tobacco in early pregnancy increased the prevalence of admission to neonatal intensive care unit at 19% and the prevalence of major congenital abnormalities by 22% with compared

non-smokers.[79] The adjusted odds ratio (OR) [95% CI] of smoking cessation after the first trimester of pregnancy was 1.2 [1.1-1.2] and 1.3 [1.2-1.3] and after the second trimester of pregnancy was 1.7 [1.6-1.8] and 1.8 [1.7-2.0], respectively, for Fetal Growth Restriction less than the 10th and fifth percentiles. While, the highest Fetal Growth Restriction Risks were for those who smoked throughout pregnancy (adjusted OR [95% CI] 2.2 [2.2-2.3] and 2.4 [2.4-2.5]).[73]

A recent systematic review carried out by Lumley et al. (2009) indicated that interventions for smoking cessation increase the mean birth weight of infants by 33 g (95% CI 11 g to 55 g) and simultaneously reduce preterm birth (pooled RR 0.84, 95% CI 0.72 to 0.98) in pregnant women who quit smoking.[80] These children growing up are more likely to have a reduced need for health care, suffer less from chronic diseases and in general benefit the health care system.[81,82]

It has been estimated that the potential neonatal cost savings that could be accrued from maternal smoking cessation during pregnancy were estimated at $881 per maternal smoker.[83] More over the health benefits for women who quit smoking are direct and last for their whole lifetime.[84] Consequently, the minimal cost invested in successful smoking cessation programmes during pregnancy and large health gains mean these interventions are highly cost-effective.[85]

RECOMMENDATIONS:

- Pregnant women should quit smoking as early as possible during the first trimester of pregnancy and stay smoke-free after birth (Level of Evidence A).

3.0
FACTORS ASSOCIATED WITH PERINATAL SMOKING CESSATION

3.1 Nicotine Metabolism during pregnancy and breastfeeding

During pregnancy the rate of nicotine metabolism may increase in a woman by an estimated 60%.17 The increased rates of nicotine metabolism during pregnancy may make it more difficult for a woman to quit smoking. Likewise the use of nicotine replacement therapy (NRT) to support cessation may require adjusted dosing to account for this increase in metabolism. At the present time there is no data about nicotine metabolism among breastfeeding woman.

3.2 Maternal Stress and Mental Health Disorders

Women who smoke during pregnancy report higher levels of perceived stress, depression, neuroticism, and negative paternal support.[86] Maternal stress, may therefore, inhibit smoking cessation during pregnancy and promote relapse after pregnancy in women who have achieved abstinence.[87] Women reporting depressive symptomatology are up to four times more likely to smoke during pregnancy than non-depressed women.[27] The use of smoking "to cope with emotions or problems" more than doubles the odds of continued smoking in pregnancy.[88] Despite these strong associations, there is limited information available about the effects of smoking and interventions in pregnant women with psychological symptoms, as they are often excluded from trials.[27] The stigmatization of smokers has been an unintended consequence and may further increase stress among pregnant women who smoke.[89] After the infant is born, postpartum stress, infant irritability, and breastfeeding failure all may contribute to continued smoking.[90]

Compared to women who continue to smoke during pregnancy and those who quit, Lopez et al. (2011) found that pregnant smokers are more likely to have current and lifetime PTSD diagnoses, have more instances

of previous abuse trauma, and are more likely to endorse having used tobacco to "cope with emotions or problems."[88] Studies with pregnant survivors of sexual abuse trauma 91 and with pregnant women with PTSD 92 find associations of abuse history and PTSD with smoking during pregnancy..

Additional factors which are known to be associated with perinatal smoking include: health inequalities, lifestyle choices, drug dependence and addiction.[93]

3.3 Partner/Significant Others Tobacco Use

Partners play an important role in influencing women's smoking behaviour in the perinatal period, either as barriers or facilitators to quitting.[94] A partner who continues using tobacco throughout a woman's pregnancy is a significant predictor of the current smoking status of the pregnant woman.[4, 6, 12 5,8,25,95] Women who do not quit smoking during their pregnancy typically come from families with smokers, had partners who smoked, or lived with relatives who smoked.[4, 96]

4.0
THE ROLE OF HEALTH PROFESSIONALS

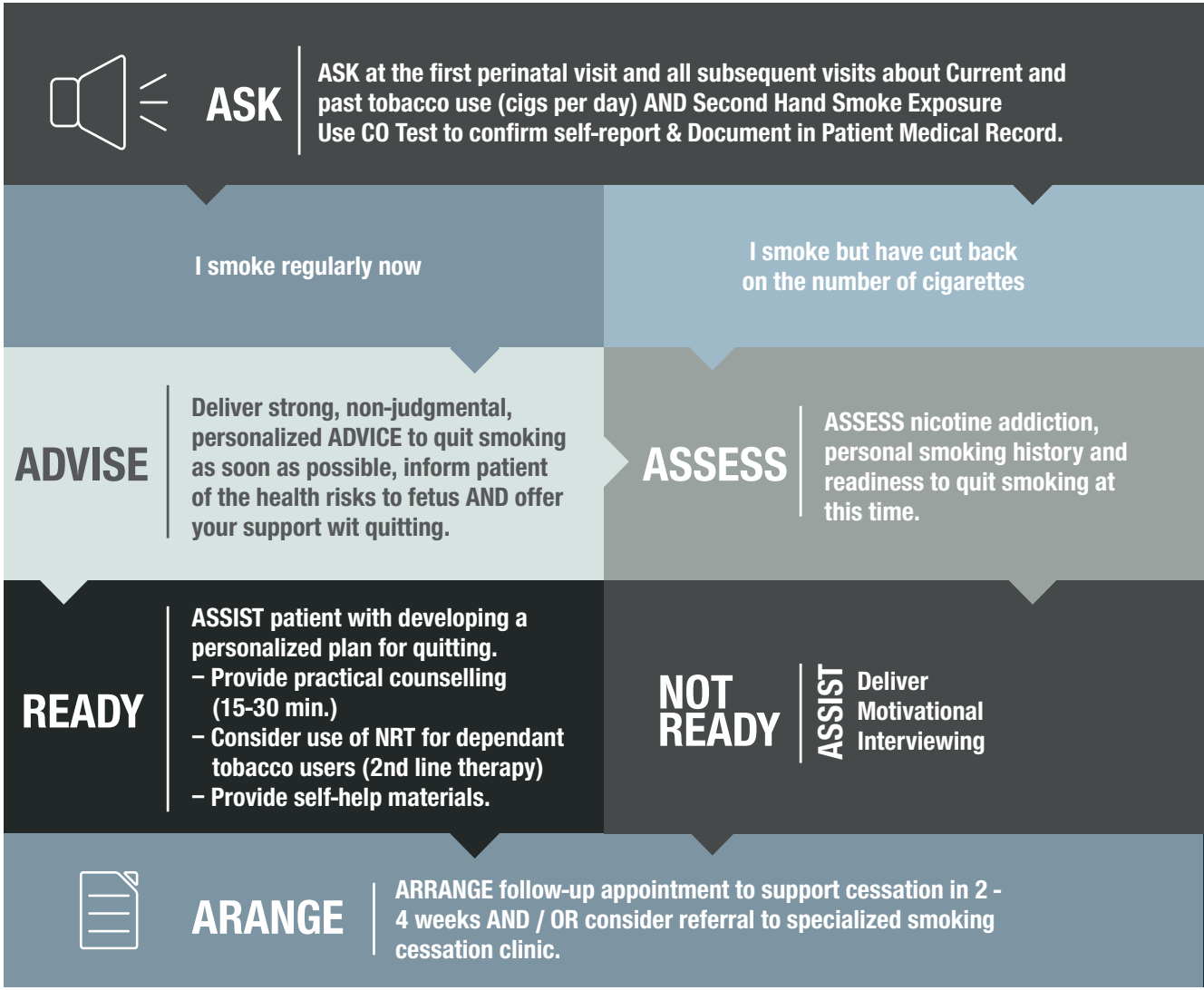
Smoking cessation is considered the "gold standard" of preventive intervention and has a powerful effect in reducing morbidity, mortality and quality of life of all tobacco users.[97] The severity of the health risk imposed to the unborn foetus and new born mean that it is even more important that health professionals working with pregnant woman including family physicians, midwives, obstetricians and gynaecologist, and nurses be familiar with the latest evidence and be comfortable intervening and supporting woman with achieving cessation. Likewise, eliminating or minimizing second-hand smoke exposure, should be aggressively addressed by all health professionals working with pregnant woman.

The increasing awareness of expectant parents about the risks of smoking on pregnancy outcomes and the health of their new born makes pregnancy a "teachable moment" in which an expectant mother's receptivity toward smoking cessation messages is increased and as such offers an important opportunity for smoking cessation.[98]

The **"5 As"** (**Ask, Advise, Asses, Assist, Arrange**) is a widely accepted model for delivering tobacco treatment in clinical settings and is appropriate for use among pregnant tobacco users (see **Figure 2**). The American College of Obstetricians and Gynaecologists recommends the "5 As" model as the intervention of choice for smoking cessation for pregnant smokers as the intervention model is both evidence-based, short and easy to use.[182] The **"5 As"** model recommends smokers are first **asked** about their smoking status at every visit and recorded in the medical record. If they have already quit smoking before or just after they found out they were pregnant, they are congratulated about their success in quitting and encouraged to stay smoke free. If they are currently smoking, brief and personal **advice** about smoking cessation and how it affects not only the foetus but also themselves should be delivered alongside an offer of support with quitting. Pregnant smokers' willingness to quit smoking within a month is then **assessed**. If pregnant women express the willingness to quit smoking, they receive **assistance** with quitting. Assistance includes the provision of self-help material, behavioural counselling, and as appropriate pharmacotherapy. Follow-up visits are **arranged** to support cessation among women making a quit attempt or a referral is made to a specialized quit smoking service.[84] Women who do not ex-

press a willingness to quit should receive intervention to examine barriers and concerns regarding quitting and follow-up should be scheduled. Setting incremental goals such as reduction of tobacco use may be appropriate among woman unwilling to quit. Referral to more intensive counselling services is recommended for woman unwilling or unable to quit.

FIGURE 2: The 5As Model for Smoking Cessation



in Pregnancy and the Post-Partum Period

ADVISE all woman and partners to ensure 100% smoke free environment at home, and other settings (restaurants, social gatherings).

I stopped when I found out I was pregnant

I stopped before I found out I was pregnant

I have never smoked

ADVISE Congratulate on success with quitting & reinforce importance of styaing quit throughout the pregnancy and the postpartum period.

ASSESS intentions for remaining smoke free postpartum.

ASSIST
- Provide behavioural counselling to support cessation during post-pardum period.
- Assess smoking status and intentions regurarly.

4.1 Midwives

Smoking cessation should be considered throughout the spectrum of care of a pregnant woman from the first visit and follow-up visits as well as following childbirth. All midwives should receive training in smoking cessation and should address tobacco use with all pregnant women as a standard practice of care. Midwives are uniquely positioned to deliver education and counselling that is more patient-centered during the antenatal and postnatal period in both clinical and community settings.[99] Midwives should provide women with evidence-based information about the risks of smoking to mother and foetus, including smoking by partners or family members.[77] At the initial and follow-up appointments midwives should record smoking status of the mother, partner and family members and use carbon monoxide (CO) breath test to validate self-reports and offer support with quitting including referral to available community-based smoking cessation services. At follow-up appointments midwives should check if referral was taken-up and provide alternatives to support cessation.

In West Scotland the development of a home-based midwifery intervention program to support young pregnant smokers to quit was a feasible approach to engaging young pregnant smokers to help them quit.[100] Local community-based midwives were found to be very willing to support this approach. [101]

4.2 Nurses

Nurses have an important role to play in smoking cessation in all health care settings.[102] There are an estimated 17 million nurses worldwide, who encounter smokers daily in their clinical routines.[103] Nurses are at the forefront of primary health care and well placed to advise all groups of tobacco users and provide cessation counselling.[104,105] A meta-analysis by Gaffney et al. included 64 published studies (1988-2009 reported a statistically significant effectiveness of nursing interventions in smoking cessation during pregnancy (OR = 1.14, 95% CI = 01.08 - 01.02).[106] Also, according to a systematic review published by Rice et al (2013), which included 35 research studies with more than 17,000 participants that compared a nursing intervention to usual care or control group, demonstrated that nursing intervention increased the likelihood of smoking cessation (RR 1.29; 95%CI 1.20 to 1.39). These results demonstrate the benefits of smoking cessation advice and counselling provided by nurses, especially by those whose main role was health promotion or smoking cessation.[107]

4.3 Primary health care – General Practice, Obstetricians & Gynaecologists

Smoking cessation in primary health care / general practice should be considered for the full spectrum of pregnancy from pre-conception visit to at least 1 year postpartum. The family planning process is a useful time to address cessation among both men and woman who are planning a pregnancy and for infertile couples who

smoke, because they could quit smoking before pregnancy. The "5 As" model should be used to guide treatment delivery. All primary care providers should be prepared to provide counselling support to expectant woman and their partners and as appropriate be knowledgeable about specialized cessation support services for smoking cessation that pregnant woman who smoke can be referred to for more intensive support. The flowchart with the procedures for smoking cessation during pregnancy at primary health care is illustrated in **Figure 4**. **Table 3** summarizes opportunities for intervention for young women smokers (15-45 years old) created by the World Health Organization.[108]

TABLE 3: Opportunities for intervention for female tobacco users ages 15-45 years

SMOKING STATUS	RECOMMENDED INTERVENTIONS
Smokers (age 15-45)	– Use policy and interventions to promote pre-pregnancy quitting.
Early pregnancy smokers	– Promote early first-trimester cessation. – Offer cessation help (5As) in obstetric care.
Early pregnancy quitters	– Provide support to maintain cessation during pregnancy and postpartum. – Promote spouse and family quitting and exposure reduction. – Shift motivation to include mother not just baby.
Late pregnancy quitters	– Provide intensive interventions to promote cessation. – Support reduction even late in pregnancy. – Involve the family in protecting the foetus and preparing for the baby.
Pregnancy quitters	– Engage family and spouse smokers to quit. – Offer relapse prevention individually postpartum.

SMOKING STATUS	RECOMMENDED INTERVENTIONS
Continuing smokers	– Prevent return to pre-pregnancy levels. – Provide interventions during paediatric visits. – Promote smoke-free home policies. ‘
Postpartum relapsers	– Support a new quit attempt and learn from past quit experience. – Promote smoke-free home policies.

Source: Adapted from Samet J M, & Yoon S Y. (2010). Gender, women, and the tobacco epidemic. Geneva, World Health Organization.[108]

4.4 Specialized Smoking Cessation Services

Specialised smoking cessation programs and services can offer more intensive counselling and support that is tailored to the needs of women who continue smoking during pregnancy, however the availability of such services as well as referral rates from health providers has been poor.[109] Major barriers of pregnant women to access such services include transportation difficulties and problems with childcare for other children, lack of time and a belief that they would not be helped but such services.[99] According to a large (n=52,370) observational study conducted in Scotland in 2005/6, 25% of pregnant women reported being current smokers at the maternity booking and 24% (3,133/13,266) were referred to specialised cessation services.[110] Fifty-eight percent of all pregnant smokers were referred to cessation support services, 11.5% were engaged in specialized services, 11% of women set a quit date and 3.5% had quit four weeks later.[110] Among woman who were ready to quit smoking, 19% engaged in service delivery, 15% set a quit date and 4.3% had quit four weeks later.[110]

RECOMMENDATIONS:

- All health professionals working with pregnant women including family physicians, midwives, obstetricians and gynecologist, and nurses should be familiar with the latest evidence and be comfortable intervening and supporting women with achieving cessation (Level of Evidence A).
- The “5 As” (Ask, Advise, Assess, Assist, Arrange) can be used as a clinical model for supporting cessation among pregnant women (Level of Evidence B).
- Health professionals should deliver strong non-judgmental advice to quit to all women who smoke and

assist tobacco users with cessation, which includes follow-up throughout the duration of the pregnancy and early postpartum period (Level of Evidence A).
- Women unable to quit smoking should receive intensive counselling and support with quitting as early as possible in their pregnancy (Level of Evidence B).
- When available women unable to quit should be referred to specialized cessation support. Health professionals should follow-up to ensure treatment is undertaken (Level of Evidence D).

5.0
ASSESSMENT OF NICOTINE USE IN PREGNANCY

The appropriate screening for tobacco exposure during pregnancy is critical. Health professionals should ensure at minimum all pregnant women are screened for:
- Second-hand smoke exposure (SHS);
- Personal tobacco use at present and prior to pregnancy (using biochemical validation when possible).

Additionally among women who report current or past tobacco use the following should be assessed:
- Nicotine Dependence (optional);
- Readiness/Motivation to Quit;

We outline here available tools for the assessment of tobacco use exposure as well as tools for the assessment of pregnant tobacco users in order to guide intervention delivery.

5.1 Assessment of Second-hand Smoke Exposure

The World Health Organization (WHO) recommends that health professionals should assess exposure to during pregnancy.[111] **Figure 3** provides a summary of recommended questions for the assessment of SHS exposure that health professionals should ask expectant parents during perinatal period. Health professionals should promote SHS avoidance behaviours and implement strategies to reduce second-hand smoke exposure in the home, car, work and social activities recognizing that smoke-free workplace legislation increases the likelihood that people (both smokers and non-smokers) will voluntarily make their homes and cars smoke-free.[111] Lee et al 2012 found most pregnant women felt powerless and lacked self-efficacy to stop others from smoking in their presence.[112]

FIGURE 3: Recommended questions for screening for second-hand smoke (SHS) exposure during pregnancy

PARTNER/SIGNIFICANT OTHERS

1. Does your partner/spouse smoke? Do they smoke in your presence?
2. Do other significant others who you have routine contact with smoke in your presence?

HOME

3. Is there a total smoke-free ban in the home?
   - Are there any exceptions to that rule?
   - Is smoking allowed in specific rooms in the home that is used by the pregnant woman?
   - Is smoking limited to part of the house where the pregnant woman rarely goes?

CAR

4. Is there a total car-smoking ban?
   - Are there any exceptions to that rule? (e.g. smoking with open window during driving)

WORK AND SOCIAL

5. Is there a smoking ban in your work place?
6. Are you exposed to smoke in your workplace?
7. Do you attempt to go places for social activities (cafes, restaurants, bars, events) where there is a smoking ban?
8. How frequently would you say you are you in places where people are smoking?

5.2 Biochemical Validation of Smoking Cessation

Research has found a high rate of misreporting of smoking status among pregnant women.[80] Walsh found the rate of false declaration of abstinence from smoking was 48% of pregnant women sampled.[113] As such, biochemical validation of smoking status is recommended for all pregnant women.[114] There are a variety of methods, which can be used, for biochemical validation including: cotinine levels in salivary samples or in urine samples, expired carbon monoxide, or by hair analysis to detect nicotine and cotinine. We briefly review each method and its relevance among pregnant woman here.

5.2.1 Expired Carbon Monoxide (CO)

Expired CO is a convenient, low-cost measurement, providing immediate results for the evaluation of smoking status. Its short half-life (3-6 hours) can lead to false negatives, as it is not able to detect tobacco use among individuals who have abstained from smoking for several hours.[115,116]

Overview of CO-Testing

- Ask about smoking status and exposure to second-hand smoke.
- Explain what the CO test is and that she will be able to see a physical measure of her smoking and her exposure to other people's smoking.
- In order to interpret the CO reading correctly ask if she is a light or infrequent smoker, how many cigarettes she has smoked on the test day and when she smoked her last cigarette.
- The best cut-off point to separate smoker and non-smoker is 7 ppm.[117]

5.2.2 Nicotine

Nicotine has a half-life of only 2-3 hours in the blood, due to its short half-life, nicotine levels can only inform us about recent exposure to tobacco smoke.[118]

5.2.3 Cotinine

Cotinine is the major metabolite of nicotine and the biomarker that determines the exposure to smoke for a longer time, because compared with the half-life of nicotine (2-3hours), it has a longer half-life (15-19 hours) in different body fluids (plasma, urine and saliva).[118] Therefore, cotinine is the biomarker of choice for both active and passive smoking exposure. [118] Because of its longer half-life, cotinine levels accumulate during the day. Furthermore, cotinine is eliminated over a longer time period than nicotine, which leads to relatively stable levels of cotinine throughout the day. [118]

However, the concentration of cotinine in the body fluids of pregnant women differs from that of the normal adult population.[119-121] Rebagliato et al. found significant differences between prenatal and postnatal cotinine concentrations in smokers after controlled smoking consumption.[119] The researchers conclude that the metabolism and distribution of nicotine and cotinine during pregnancy is modified, with higher rates of clearance of cotinine compared with those of non-pregnant smokers.[121]

A new method of biochemical validation uses hair analysis; depending on the length of the hair, this method provides information about the smoking status during the last six months, as hair grows approximately 1 cm per month.[122] Klein et al analysed hair samples from the scalps of 28 pregnant women, who reported that they smoked the same amount during all three trimesters of pregnancy, to find that indeed there is an increase in nicotine metabolism in pregnancy.[123] However, cotinine remained steady throughout pregnancy in the analysis. Therefore, the levels of cotinine should be examined as they provide a more reliable history of exposure to active smoking. On the other hand, a decreased concentration of nicotine should be treated with caution, taking into account the increase in its metabolism.

5.3 Fagerström Test For Nicotine Dependence (FTND)

The Fagerström Test For Nicotine Dependence (FTND) is a brief and widely used 6-item questionnaire used to evaluate the level of nicotine dependence among tobacco users (See **Figure 4**).[124] The FTND measures both behavioural and physiological aspects of addiction (e.g. the rate of smoking, smoking in the morning, and difficulty in abstaining from smoking).[125,126] The FTND score is calculated based on the ranking of responses on a scale from 0-10. Score of 7 to 10 indicates the maximum nicotine dependence, 4-6 moderate dependence and

less than 4 indicates minimal dependence.[124]

FTND can be used to determine the appropriate initial dosing of nicotine replacement therapies and can potentially predict the need for more intensive cessation support.[124] Berlin et al 2015 examined the FTND in a sample of pregnant smokers (n=476). Results demonstrate that the Cronbach's alpha coefficient for the FTND was 0.55 and that FTND was associated with saliva cotinine concentration, but failed to anticipate smoking status two weeks after smoking cessation.[127] A recent systematic review of Yang and Hall (2016) that included fifty-five studies provides an analysis of nicotine dependence measures used for smoking cessation perinatally and their psychometric properties. The majority of the studies had used the FTND, however this review demonstrated that FTND might not be the best way for measuring nicotine dependence in this specific population suggesting future research to assess its reliability during pregnancy and postpartum period.[128]

FIGURE 4: Fagerström Test for Nicotine Dependence (FTND)

1. How soon after you wake up do you smoke your first cigarette?

Within 5 minutes	3 points
5 to 30 minutes	2 points
31 to 60 minutes	1 point
After 60 minutes	0 points

2. Do you find it difficult not to smoke in places where you shouldn't, such as in church or school, in a movie, at the library, on a bus, in court or in a hospital?

Yes	1 point
No	0 points

3. Which cigarette would you most hate to give up, which cigarette do you treasure the most?

The first one in the morning	1 point
Any other one	0 points

4. How many cigarettes do you smoke each day?

10 or fewer	0 points
11 to 20	1 point
21 to 30	2 points
31 or more	3 points

5. Do you smoke more during the first few hours after waking up than during the rest of the day?

Yes	1 point
No	0 points

6. Do you still smoke if you are so sick that you are in bed most of the day, or if you have a cold or the flu and have trouble breathing?

Yes	1 point
No	0 points

SCORING: 7 to 10 points = highly dependent | 4 to 6 = moderately dependent | less than 4 points = minimally dependent

Source: Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström test for nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991;86:1119–27. [129]

5.4 Assessment of Motivation to Quit

Motivation / readiness to quit smoking should be assessed in all pregnant tobacco users. Tools such the readiness to quit ladder (see Figure 5) which asks pregnant smokers to assess their readiness to quit on a scale for 1 to 10 are a useful tool for understanding readiness to quit and tailoring interventions based on the current readiness of the tobacco user (See section 6.2 Stages of Change).

FIGURE 5: Readiness to Quit Ladder

10	I have quit smoking.
9	I have quit smoking, but I still worry about slipping back, so I need to keep working on living smoke free.
8	I still smoke, but I have begun to change, like cutting back on the number of cigarettes I smoke. I am ready to set a quit date.
7	I definitely plan to quit smoking in the next 30 days.
6	I definitely plan to quit smoking in the next 6 months.
5	I often think about quitting smoking, but I have no plans to quit.
4	I sometimes think about quitting smoking, but I have no plans to quit.
3	I rarely think about quitting smoking, and I have no plans to quit.
2	I never think about quitting smoking, and I have no plans to quit.
1	I have decided not to quit smoking for my lifetime. I have no interest in quitting.

Source: Abrams DB, Niaura R, Brown RA, Emmons KM, Goldstein MG, Monti PM. The Tobacco Treatment Handbook: A Guide to Best Practices. New York: Guilford Press, 2003 (page 33). Adapted by the Center For Tobacco Independence.[130]

RECOMMENDATIONS:

- All pregnant women should have both their smoking status and second-hand smoke exposure assessed as part of routine examinations (Level of Evidence A).
- It is recommended that tobacco use be biochemically assessed at antenatal and postnatal visits to determine smoking status (Level of Evidence A).
- When available, the use of urine or saliva cotinine tests is recommended, as they are more accurate than CO tests and detect tobacco exposure over the past few days rather than few hours (Level of Evidence A).

6.0
COUNSELLING INTERVENTIONS FOR SMOKING CESSATION DURING PREGNANCY

Counselling interventions for smoking cessation during pregnancy can serve to enhance motivation to quit, guide to problem solving and increase coping skills.[131] The 2016 ENSP Guidelines for Treatment of Tobacco Dependence identifies three categories of behavioral counselling interventions: psychological support for smoking cessation, cognitive-behavioral therapy (CBT) and motivational interviewing (MI). All three intervention approaches have common elements, to treat psychological and behavioral dependence of tobacco users.

A variety of formats have been tested for delivering non-pharmacologic smoking cessation treatments including: individual counselling, proactive telephone counselling, group counselling, web-based, and self-help in the general population. Counselling interventions, which may be used during pregnancy, are summarized in **Figure 6**.

FIGURE 6: Examples of Individual psychosocial interventions to support cessation during pregnancy

- > Individual behavioural counselling
- > Motivational interviewing
- > Stage-based interventions,
- > Telephone counselling
- > Mobile phone-based interventions
- > Internet-based interventions
- > Incentives
- > Health professional advice
- > Enhancing partner support
- > Training health professionals in smoking cessation
- > Relapse prevention

Source: Chamberlain C, et. al. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database of Systematic Reviews 2017. No.: CD001055.[27]

6.1 Cognitive Behavioural Interventions

Cognitive behavioural interventions are a well-accepted counselling model and have been widely used in smoking cessation in both the general population and among pregnant woman.[27] Cognitive behavioural interventions aim to change an individuals' tobacco use by changing habitual ways of thinking and feelings about smoking and oneself and provides encouragement and advice on ways of minimizing and managing the desire to smoke. Cognitive behavioural interventions have been used to support cessation in pregnant smokers with positive results.[114,132-134]

A 2017 Cochrane review by Chamberlain found high quality evidence that among pregnant woman who smoke, counselling significantly increased smoking cessation in late pregnancy compared with usual care (30 studies; average risk ratio (RR) 1.44, 95% confidence interval (CI) 1.19 to 1.73), and less intensive interventions (18 studies; average RR 1.25, 95% CI 1.07 to 1.47).[27] The effect on smoking abstinence was further broken down

by time point postpartum. A significant effect was found at zero to five months postpartum (11 studies; average RR 1.59, 95% CI 1.26 to 2.01), a borderline effect at six to 11 months (6 studies; average RR 1.33, 95% CI 1.00 to 1.77), and a significant effect at 12 to 17 months (2 studies, average RR 2.20, 95% CI 1.23 to 3.96).27 High-quality evidence was found which indicates that women who received psychosocial interventions had a 17% reduction in infants born with low birth weight, a significantly higher mean birth weight (mean difference (MD) 55.60 grams, 95% CI 29.82 to 81.38 grams higher) and a 22% reduction in neonatal intensive care admissions.[16] The difference in preterm births and stillbirths was unclear.

In most studies an intensive intervention lasting more than 15 minutes was found to be more effective than the shorter and less individualized interventions, which are described in some studies as "low intensive intervention" and in others as "usual care" (<5 minutes).[114,134,135] Perhaps this is also due to the fact that some studies included communication for a period of time after childbirth and final biochemical measurement after 2-6 months.[136,137] A systematic review and meta-analysis by Melvin et al. examined the most effective counselling interventions for smoking cessation during pregnancy and also found that more intensive intervention is more effective.[84] Authors propose that the duration of this intervention be about 15 minutes, that counselling use cognitive behavioural approaches and be accompanied by printed material.[84]

RECOMMENDATIONS:

- Counselling-based interventions are effective in supporting cessation among pregnant women (Level of Evidence A).
- Counselling interventions are effective in significantly reducing low birth weight, increasing mean birth weight, and reducing neonatal intensive care admissions (Level of Evidence A). The effect of counselling intervention on pre-term births and stillbirths is unclear (Level of Evidence C).
- Intensive cognitive behavioural interventions are more effective in supporting cessation among pregnant women (Level of Evidence A).

6.2 The "Stages of Change"- Transtheoretical Model

The well-known "stages of change" proposed by Prochaska and DiClemente transtheoretical model have also been used to deliver counselling based interventions.[138] According to this model a person may go through five stages of change, when trying to change their behaviours and it is recommended that intervention strategies be tailored to the stage in which each smoker finds herself (See **Table 4**).[138] The first stage that is "pre-contemplation" in which there is indifference about smoking cessation and tobacco user's may show resistance with recognizing the problem behaviour.[138] At the second stage, that is named "contemplation", the health professional investigates whether there is a concern about smoking cessation that needs to be strengthened. The basic characteristic of someone at the contemplation

stage is that the person at this stage is seriously thinking about resolving the problem.[139] The third stage is the stage of "planning and preparation" that indicates that there is a desire to quit smoking in the next 30 days.[117] The fourth stage is called "action" because during this stage the decision for smoking cessation is implemented. At this fourth stage smoking cessation is a fact and efforts are made to prevent smoking relapse.[138] The final stage is called "maintenance" because its objective is the maintenance of abstinence from smoking without the occurrence of relapse.

TABLE 4: The "Stages of Change" and associated intervention strategies

STAGE OF CHANGE	DESCRIPTION
1. Pre-contemplation	no intention to quit
2. Contemplation	thinking about quitting
3. Planning and preparation	planning to quit in the next 30 days
4. Action	successful quitting for up to 6 months
5. Maintenance	smoke-free for more than six months

Source: European Smoking Cessation Guidelines: The authoritative guide to a comprehensive understanding of the implications and implementation of treatments and strategies to treat tobacco dependence. Revised 1st edition. October 2012 pp49.[117]

The "stages of change" counselling strategy for smoking cessation has been used to investigate the effectiveness of brief intervention (10-15 minutes) for smoking cessation in pregnancy provided by hospital staff in routine conditions.[136] Pregnant women who did not want to stop received brief intervention in order to be motivated. Those who wanted to quit smoking received support. At the same time, those who had already quit smoking received an intervention to help them avoid smoking relapse. The intervention was not found to be effective in increasing cessation.[136]

An RCT by Lawrence et al. compared the effectiveness of interventions based on the "stages of change" with those provided with standard care. This survey involved 918 pregnant women, who were divided into three groups.[140] The first group received routine care, the second group received self-help manuals based on the transtheoretical model of "stages of change", while the third group received the same intervention as the second group along with a computer-based educational program with personalized advice on smoking cessation. Ten days after child birth, 3.5% of the first group, 4.7% of the second group and 8.1% of the third group had stopped smoking.[140] The combination of educational methods in the intervention proved to be most effective.

Despite the popularity of the stages of change model there is no strong evidence to support its use.

6.3 Evidence for Various Intervention Approaches

6.3.1 Individual interventions

Individual counselling interventions demonstrated a significant effect compared with usual care condition (27 studies; (RR) 1.44, 95% (CI) 1.19 to 1.75).27 Previous Cochrane reviews have also indicated the potential for individual interventions during pregnancy to have a moderate but significant effect on reducing smoking in pregnancy, preterm births and infants' low birth weight.[80]

RECOMMENDATION:

- Person-to-person psychosocial interventions that exceed minimal advice to quit should be offered to pregnant smokers (Level of Evidence A).

6.3.2 Social Support and Group Interventions

Social support interventions appeared effective when provided by peers (five studies; RR 1.49, 95% CI 1.01 to 2.19).[27] Group interventions may include health education information about the risks of smoking and advice to quit, and support or advice about how to make this change.[27] During the group interventions the mother may be provided with feedback about foetal health status or measurement of tobacco smoke exposure to reinforce behaviour change.[27] This includes ultrasound monitoring and CO or urine cotinine measurements, with results fed back to the mother.[27] Finally, group intervention may also include exercise, weight control, alternative therapies etc.[27]

RECOMMENDATION:

- Group based interventions of sufficient intensity have a modest but positive effect in increasing smoking abstinence among pregnant women (Level of Evidence B).

6.3.3 Partner-based interventions

Partner-based interventions for smoking cessation have not been well evaluated but may be useful in particular when both partners are tobacco users.[27] One randomized controlled trial has evaluated couple-based support intervention to assist women's smoking cessation during pregnancy increased women's abstinence rates during and after pregnancy compared to usual care and a previously evaluated woman-only intervention.[141] Although the couple-based intervention did not significantly improve abstinence rates over usual care, the results

suggest the feasibility of couple-based interventions and further research is required to understand the value of partner-based therapy. [141]

RECOMMENDATIONS:

- There is very limited research regarding partners-based interventions to support smoking cessation and additional research is required to better understand the value of such interventions (Level of Evidence C).

6.3.4 Quitlines

Smoking Cessation quitlines offer telephone-based advice and counselling from trained smoking cessation specialists. These services can be offered when available to support cessation among pregnant woman. A meta-analysis of seventy-seven trials found in the general population of tobacco users that proactive telephone counselling of three or more calls to be more effective than a minimal intervention/brief advice.[142] Quitlines in the USA as well as the United Kingdom, offer a pregnancy tailored quit smoking protocol in which trained staff deliver counselling to support prenatal smoking cessation and postpartum relapse.[183] Bombard et al. (2013) examined the characteristics, service utilization and the self-reported quit rates among 1,718 pregnant and 24,321 non-pregnant smokers, who enrolled in quitline services from 2006 to 2008 in 10 states in USA.[143] Seven months after enrolment in quit-line services the self-reported quit rates were 26.4% for pregnant women and 22.6% for non-pregnant women.[143] In many countries, health care systems and health professionals have become partners with quitlines and refer patients regularly. Engaging health professionals in referring their patients to smoking cessation to quitline services, is a form of complementary service delivery in which health professionals identify and advise patients to quit smoking and refer patients for more intensive counselling to the quitlines.[144] Some health professionals might be more willing to refer to quitlines following a proactive enrolment model, where the patients' (who agree to be contacted by a counsellor) are referred to the quitline, who initiates contact with the patient.[145]

RECOMMENDATIONS:

- A tailored quit smoking protocol for prenatal smoking cessation and postpartum relapse delivered by trained counsellors, should be offered by all quit-lines services (Level of Evidence D).
- Proactive telephone counselling of 3 or more calls may be more effective than a minimal intervention (Level of Evidence B).

6.3.5 Incentives

The use of incentives to encourage smoking cessation among pregnant woman has been examined in recent literature. A recent review by the Cochrane Collaboration identified high quality evidence that incentive-based intervention were effective compared to non-contingent incentives (4 studies; RR 2.36, 95% CI 1.36 - 4.09).[27] An earlier meta-analysis by Higgins 2010 identified three trials (n=166) in which pregnant tobacco users were randomized to receive vouchers for retail goods based on abstinence from smoking compared to controls (no incentive).[146] The vouchers began at $6.25 and increased to a maximum of $45. The incentive group had significantly greater rates of smoking abstinence in late pregnancy (34.1% vs. 7.4%, P < 0.001), higher mean birth weight (3295 g vs. 3093 g, p = 0.03) and fewer babies with a birth weight< 2500 g (5.9% vs. 18.5%, p = 0.02). Interestingly, the effect on smoking abstinence was no longer significant when the vouchers were discontinued postpartum. In a small study, Donatelle et al. (2000) found similar rates of smoking abstinence in late pregnancy and increased rates of abstinence two months postpartum when both the patient and a "social supporter" received vouchers as an incentive to smoking abstinence compared to controls.[147]

The use of incentives to support cessation is a promising intervention strategy for supporting cessation among the population of pregnant smokers. Further research is needed to increase the strength and generalizability of this evidence.

RECOMMENDATIONS:

- The use of incentives is a promising intervention strategy for supporting smoking cessation among pregnant smokers however more research is required to strengthen this recommendation (Level of Evidence B).

6.3.6 Health Education and Self- help manuals

Self-help materials have been shown to be effective in a number of RCTs involving pregnant woman.[133,148] Self-help materials are defined as structured materials (printed or audio-visual) that assist the individual in making an attempt to quit and sustaining abstinence without significant assistance from health professionals.[149] In most studies a self-help manual is an informative booklet; after it has been presented and explained, the pregnant woman takes it with her and can read it as many times as she wishes and refer to it whenever necessary. A self-help manual is not limited to information about the effects of smoking on the foetus, the potential complications during pregnancy and adverse outcomes in childbirth, but also includes the effects of smoking on women's health in order to prevent a smoking relapse postpartum.

According to Chamberlain et al., the provision of self-help materials in pregnant women offered a modest but significant effect (RR 1.21, 95% CI 1.05 to 1.39), materials that were tailored for pregnant women were more effective than general materials (RR 1.31, 95% CI 1.20 to 1.42).[27]

RECOMMENDATIONS:

- The provision of self-help manual can have a modest but significant effect for supporting smoking cessation in pregnancy (Level of Evidence A).
- Information in the self-help manual should include the health effects of smoking on the foetus, the potential complications during pregnancy and adverse outcomes in childbirth, but also include the effects of smoking on women's health in order to prevent a smoking relapse postpartum and strategies to support cessation.

6.3.7 Internet-based Interventions

The use of the Internet in smoking cessation is a new and promising category of smoking cessation interventions and given the high rates of Internet use among pregnant woman may offer significant reach.[150] Online smoking cessation interventions seem to be suitable for pregnant smokers, because they offer non-judgmental and flexible help that is valued by pregnant smokers[151], and can be offered remotely.[152] Internet-based smoking cessation interventions offer the available treatment and close monitoring of behaviour and progress that might be especially helpful for smoking cessation for pregnant women.[153]

A new internet-based intervention focusing on smoking cessation in pregnancy named 'MumsQuit' deliveres fully automated cessation support.[154] In a pilot RCT evaluation, pregnant adult smokers (n=200) were randomized to either the "MumsQuit" intervention or a website that provided only information. The study found that participants in the 'MumsQuit' group logged in more often (3.5 vs. 1.3, $p<0.001$), viewed more pages (67.4 vs. 5.7, $p < 0.001$) and spent more time browsing the specific website (21.3 min vs. 1.0 min, $p < 0.001$) than the control group.[154]

A systematic review of Civljak et al. (2013) examined the effectiveness of Internet-based interventions for smoking cessation in the general adult population and found that some Internet-based interventions, especially those that are tailored and provide repeated automated contacts with the users can be effective in supporting cessation.[155] However these trials did not demonstrate consistent effects and did not specifically examine interventions for pregnant woman.[155] As such, future research is needed about the effectiveness of online smoking cessation interventions in pregnancy.

RECOMMENDATIONS:

- Internet-based Interventions for pregnant smokers are useful as they are flexible and non-judgmental, but their effectiveness has not been well documented at present (Level of evidence C).

6.4 Relapse Prevention in the Postpartum Period

Mothers who quit smoking during pregnancy remain at high risk for smoking relapse during the postpartum period. Women that have had a smoke free pregnancy should be offered help to remain smoke free after birth.[76,77] Counselling interventions used during pregnancy may not be the most effective in the postpartum period.[156,157] Culturally appropriate smoking cessation interventions should be a high priority. [92,99]

Postpartum cessation intervention strategies tested to date have documented great variation in terms of success and a broad range of relapse rates.[158] Research shows that reasons for continued cessation are related to the baby, whereas disadvantages for stopping are related to the mother.[158]

The postpartum hospitalization presents a widow of opportunity ("teachable moment") to screen and support the early identification of both mothers and fathers who currently smoke and recent quitters who may be at risk of relapse and connect them with tobacco treatment services in both the health care setting and the community. Research has found the majority of parents accepted tobacco treatment services during the hospital stay.[90]

RECOMMENDATIONS

- Parents should be encouraged to remain smoke-free in the postpartum period. Postpartum care should address relapse prevention in addition to cessation strategies for both parents before hospital discharge and during post-natal home visits (Level of Evidence A).
- Parents, who continue to smoke at the time their babies are admitted to neonatal intensive care units (NCIU), should be referred to local smoking cessation programs (Level of Evidence C).
- There is a need for more research on prevention of postpartum smoking relapse for both parents.

6.5 Interventions for reducing Second-hand Smoke (SHS) Exposure

While evidence remains scarce there have been some recent studies that report on interventions to reduce SHS among pregnant woman. According to a multi-component intervention, SHS reduction during pregnancy may reduce the risk of preterm birth.[159] A RCT by Blaakman et al (2015) found motivational interviewing was effective in reducing SHS exposure at home (home/car smoking bans and reduction in infant contact with smokers) after discharge from the NICU, however the effects of the intervention were only significant in the short-term (up to eight months post-discharge).[160]

Interventions to reduce perinatal SHS exposure needs to be tailored to the specific community settings, social support networks, and cultural assets of families within the European Union. Community-based interventions like home visits during perinatal period may be helpful in reducing SHS perinatal exposure especially for the high-risk groups like premature infants. 160 Policy-based interventions like smoke-free legislation or tobacco taxation are associated with reduced SHS exposure.[161,162]

RECOMMENDATIONS

- Health care professionals should assist with addressing SHS exposure during perinatal period by enforcing home smoking bans and reducing contact with smokers especially for infants (Level of Evidence A).
- Pregnant women's social support network, including her spouse and close family should be involved in supporting smoke-free environments in spaces shared by the new born (Level of Evidence D).

7.0
QUIT SMOKING MEDICATIONS

First-line quit smoking medications for the general population of smokers include nicotine replacement therapy (NRT), bupropion and varenicline. These medications are widely and effectively used outside of pregnancy. However, there is less evidence in terms of their efficacy and enough safety when used by pregnant smokers in order to help them quit smoking.[28] Summarized here are evidence and recommendations for each of the three first-line therapies for woman during pregnancy and the postpartum period.

7.1 Nicotine Replacement Therapy (NRT)

NRT is used to assist with reducing cravings and withdrawal symptoms related to quitting. NRT dosing is gradually reduced over time. NRT is available in the form of a long-acting patch, and short-acting gum, inhaler, spray and lozenge. NRT has been shown to double quit rates in the general population of tobacco users and triple quit rates when two forms of NRT are used in combination.[164]

Efficacy of NRT in pregnancy

Evidence on the effectiveness of NRT in helping women to quit smoking during pregnancy is mixed. The 2015 Cochrane Review by Coleman identified eight studies (2199 participants), which tested the efficacy of NRT among pregnant woman.[28] The pooled analysis found the use of NRT in combination with behavioural support was effective in supporting abstinence in pregnancy (RR 1.41, 95% CI 1.03 to 1.93). However a lower RR was found when only the higher quality of placebo-controlled trials were analysed (RR 1.28, 95% CI 0.99 to 1.66, five studies, 1926 women).[28] Four RCTs, which used NRT patches for smoking cessation in pregnancy for limited hours and behavioural counselling versus placebo NRT patches or only cognitive behavioural counselling, did not find a statistically significant effect on smoking abstinence.[28] The review also examined the use of NRT on maintenance of cessation after birth. A comparison of NRT placebo or non-placebo controlled trials did not find a significant effect of NRT when used alone for smoking cessation six months after childbirth

(RR for cessation with NRT versus placebo 1.15, 95% CI 0.75 to 1.77).[28] Importantly very low adherence to NRT was reported among trials of pregnant woman, which may limit our understanding of the effects of this therapy in this population.[28]

Safety of NRT in pregnancy

The 2015 review by Coleman found no evidence that the use of NRT for smoking cessation in pregnancy had either a beneficial or harmful effect on birth outcomes.[28] This review included six randomized studies that enrolled 2,068 women. The review found that there were no statistically significant differences between NRT or control groups in rates of miscarriage (RR 1.47,95% CI 0.45 to 4.77, four studies, 1782 Women), still birth RR 1.24, 95% CI 0.54 to 2.84, four studies, 1777 women), premature birth (RR 0.87, 95% CI 0.67 to 1.14, six studies, 2048 women), low birth weight (RR 0.74, 95% CI 0.41 to 1.34, six trials, 2037 women), admissions to neonatal intensive care (RR 0.90, 95% CI, 0.64 to 1.27, four studies, 1756 women), or neonatal death (RR 0.66, 95% CI 0.17, 2.62, four studies, 1746 women).[28]

A double-blind study by Oncken and colleagues (2008) found beneficial birth outcomes in the NRT group. Infants of nicotine gum group had greater birth weight than the control group (3287 g and 2950 g, respectively $p<.0001$) and gestational age was also increased at NRT group than control group 38.9 week and 38.0 week respectively ($p=.014$).[184] Considering the increased morbidity and mortality, which is associated with low birth weight, these birth outcomes are clinically significant. The above results are consistent with Wisborg et al. (2000) clinical trial about nicotine patches for pregnant smokers.[185] This trial reported a higher mean birth weight (by 186 g 95% CI 35, 336 g) in the NRT group compared with the placebo group.

One of the most recent and largest studies that has been published to date about the use of NRT and the major congenital anomalies (MCA) in offspring involved 192,498 children from the UK. [163] The study found no statistically significant increased risks in the most system-specific MCAs associated with maternal NRT prescribed during pregnancy, except for respiratory anomalies (OR: 4.65 [99% CI: 1.76–12.25].

Risk Benefit to NRT Use

When determining the appropriateness of using NRT for cessation among pregnant women, clinician's should consider both the risks and benefits. While the use of NRT exposes pregnant women to small doses of nicotine, active smoking exposes woman not only to nicotine, but also to numerous other chemicals that are harmful to both the woman and her foetus.[164]

Table 5 provides a summary of international guideline recommendations regarding the use of NRT to support cessation during pregnancy. The general consensus at the present time is that NRT is preferred to continued smoking if the pregnant smoker is unable to quit. Given the absence of clear data to indicate the efficacy of

NRT in supporting cessation among pregnant women it is not recommended as a first line pharmacotherapy.[165] The American College of Obstetricians and Gynaecologists has recommended that the use of NRT during pregnancy should be made after careful assessment and monitoring, and provided that a pregnant woman is determined to quit smoking.[186]

Pregnant smokers should be informed about the risks of continued smoking during pregnancy, as well as the potential risks of using NRT and a decision made in terms of use of NRT based on the risk-benefit.[29] This recommendation is based on the understanding the NRT use is inherently less dangerous than the continuation of cigarette smoking.[166,167]

Given the lack of definite safety and efficacy data, many guidelines have advised limiting the duration of patch use (i.e. 16 hours versus 24 hours) or to use intermittent dosing forms of NRT (i.e. gum, lozenge, spray or inhaler).[18,19,19,29] While this is a logical approach to reducing levels of nicotine, trials, which have tested the use of NRT for limited hours, found no effect on cessation rates.[17] Given that during pregnancy women metabolize nicotine faster, it is unclear whether lower and/or intermittent doses of NRT are effective.[168]

Further research is needed on NRT efficacy and safety, ideally from placebo-controlled RCTs.[17]

RECOMMENDATIONS

- The use of Nicotine replacement therapy (NRT) is preferred to continued smoking during pregnancy. Evidence in terms of its effectiveness among pregnant women is however mixed. As such, NRT can be considered a second-line therapy for pregnant women who are unable to for quit with counselling support alone (Level of Evidence B). The risk and benefits of using NRT should be discussed with pregnant smokers.

TABLE 5: Summary of international clinical practice guidelines regarding the use of nicotine replacement therapy (NRT) during pregnancy and the postpartum period

SOURCE	RECOMMENDATIONS
American College of Obstetricians and Gynaecologists Committee, Opinion No. 471. Smoking cessation during pregnancy. (2010)[186]	"The use of nicotine replacement therapies should be undertaken with close supervision and after careful consideration and discussion with the patient of the known risks. If nicotine replacement is used, it should be with the clear resolve of the patient to quit smoking."
New Zealand Ministry of Health Background and Recommendation of the New Zealand Guidelines for Helping People to Stop Smoking. Providing stop-smoking support to pregnant and breastfeeding women (2014)[76]	Indicates that pregnant or breastfeeding women can use NRT.
US Clinical Practice Guidelines U.S. Department of Health and Human Services. Treating Tobacco Use and Dependence (2008)[164]	"Although the use of NRT exposes pregnant women to nicotine, smoking exposes them to nicotine plus numerous other chemicals that are injurious to the woman and foetus"
CAN-ADAPTT Canadian Smoking Cessation Guideline Version 2.0: Specific Populations: Pregnant and Breastfeeding Women (2011)[169]	"If counselling is found ineffective, intermittent dosing nicotine replacement therapies are preferred over continuous dosing of the patch after a risk-benefit analysis."
UK NICE public health guidance 26 (2010) Quitting smoking in pregnancy and following childbirth (2010)[77]	"There is mixed evidence on the effectiveness of NRT in helping women to stop smoking during pregnancy. Use only if smoking cessation without NRT fails."

7.2 Bupropion

Bupropion is a non-nicotine therapy for smoking cessation available in tablet form, by prescription only. Bupropion has been found to mimic the effect of cigarette-derived nicotine by inhibiting the re-uptake of noradrena-

line and dopamine and is thought to reduce nicotine withdrawal also by this mechanism.

There is very limited information regarding the safety and efficacy of bupropion among pregnant women.[17,170,170] There has been only one RCT published about the use of bupropion for smoking cessation during pregnancy, which due to recruitment challenges randomized only 11 pregnant women.[171] Two prospective studies have been published looking at the use of bupropion in pregnancy. A small prospective controlled observational study (n=44) of pregnant smokers who received bupropion and a control group found that 45% of women in the bupropion group quit smoking compared to 14% in the control group (p=0.047).[172] A second prospective comparative study examined pregnancy outcomes among women exposed to bupropion during pregnancy.[173] No statistically significant differences were found between the examined end points of the exposed and non-exposed groups. However, higher rates of spontaneous abortions were documented in the bupropion group (p=0.009). These findings are similar to the safety data available for the use of antidepressants during pregnancy. Further research in this area is needed to better understand the role of bupropion as a cessation aid during pregnancy. At the time of this guidelines preparation there were two trials of bupropion in pregnancy currently under way.[174,175]

RECOMMENDATION

- Bupropion is not recommended for smoking cessation during pregnancy (Level of Evidence C).

7.3 Varenicline

Varenicline is a tablet-based medication that acts on the nicotine receptors in the brain. Varenicline is a partial agonist, offering a two-pronged approach to treating nicotine addiction by reducing the symptoms of nicotine withdrawal, while simultaneously reducing some of its rewarding effects of nicotine use.[176] The medication is typically taken by prescription for 12-26 weeks. While Varenicline is a first line quit smoking medication for the general population of tobacco users, there are currently no trials that report on the safety or efficacy of varenicline use during pregnancy.[17,20,177]

One clinical trial is currently under way to assess the safety of varenicline in pregnancy and to identify the risks of major malformations and other undesirable pregnancy outcomes; this study had not been completed at the time of this guideline's preparation.[176] Further research in this area is needed.

RECOMMENDATION

- Varenicline is not recommended for smoking cessation during pregnancy (Level of Evidence - None).

1. Kramer M.S. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ. 1987;65(5):663-737.
2. Kleinman JC, Pierre MB J, Madans JH, Land GH, Schramm WF. The effects of maternal smoking on fetal and infant mortality. . Am J Epidemiol. 1988;127(2):274-82.
3. Ventura S MJ, Taffel S, Mathews T, Clarke S. . Advance report of final natality statistics,. Monthly Vital Stat Rep 1995;44((suppl 5) 44):1-88.
4. Lai M.C., Chou F.S., Yang Y.J., Wang C.C., Lee M.C. Tobacco use and environmental smoke exposure among taiwanese pregnant smokers and recent quitters: Risk perception, attitude, and avoidance behavior. Int J Environ Res Public Health. 2013;10(9):4104-16.
5. Lawrence W.T., Haslam C. Smoking during pregnancy: Where next for stage-based interventions? J Health Psychol. 2007;12(1):159-69.
6. Leonardi-Bee J., Jere M.L., Britton J. Exposure to parental and sibling smoking and the risk of smoking uptake in childhood and adolescence: A systematic review and meta-analysis. Thorax. 2011;66(10):847-55.
7. Miyake Y., Tanaka K., Arakawa M. Active and passive maternal smoking during pregnancy and birth outcomes: The kyushu okinawa maternal and child health study. BMC Pregnancy Childbirth. 2013;13:157-2393-13-157.
8. Nordentoft M, Lou HC, Hansen D, et al. Intrauterine growth retardation and premature delivery: The influence of maternal smoking and psychosocial factors. Am J Public Health. 1996;86(3):347-54.
9. Pallotto EK, Kilbride HW. Perinatal outcome and later implications of intrauterine growth restriction. Clin Obstet Gynecol. 2006;49(2):257-69.
10. Vardavas CI, Chatzi L, Patelarou E, et al. Smoking and smoking cessation during early pregnancy and its effect on adverse pregnancy outcomes and fetal growth. Eur J Pediatr. 2010;169(6):741-8.
11. Blaakman S, Borrelli B, Wiesenthal E, al. e. Secondhand smoke exposure reduction after NICU discharge: Results of a randomized trial. Acad Pediatr. 2015;15(6):605-12.
12. El-Mohandes AA, Kiely M, Blake SM, Gantz MG, MN. E-K. An intervention to reduce environmental tobacco smoke exposure improves pregnancy outcomes. Pediatrics. 2010;125(4):721-8.
13. Wagijo MA, Sheikh A DL, JV. B. Reducing tobacco smoking and smoke exposure to prevent preterm birth and its complications. Paediatr Respir Rev. 2015.
14. General ARotS. The Health Consequences of Involuntary Exposure to Tobacco Smoke. Atlanta (GA): Centers for Disease Control and Prevention (US). 2006.

REFERENCES

15. Leonardi-Bee J., Britton J., Venn A. Secondhand Smoke and Adverse Fetal Outcomes in Nonsmoking Pregnant Women: A Meta-analysis. Pediatrics. 2011;127(4).
16. Euro-Peristat. European perinatal health report: The health and care of pregnant women and babies in europe in 2010. 2013.
17. Dempsey D., Jacob P., Benowitz N.L. Accelerated metabolism of nicotine and cotinine in pregnant smokers. J Pharmacol Exp Ther. 2002;301(2):594-59.
18. Saraiya M, Berg CJ, Kendrick JS, Strauss LT, Atrash HK, YW. A. Cigarette smoking as a risk factor for ectopic pregnancy. Am J Obstet Gynecol. 1998;178(3):493-8.
19. HealthHealth CoE. Committee on Substance Abuse, Committee on Adolescence, Committee on Native American Child. From the american academy of pediatrics: Policy statement--tobacco use: A pediatric disease. Pediatrics. 2009;124(5):1474-87.
20. U.S. Department of Health and Human Services (USDHHS). How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the surgeon general. 2010.
21. Centres for Disease Control (CDC). Cigarette smoking-attributable mortality and years of potential life Lost—United states. morbidity and mortality weekly report. 1993.
22. USDHHS. The health benefits of smoking cessation. A report of the surgeon general. 1990.
23. McBride C.M., Emmons K.M., Lipkus I.M. Understanding the potential of teachable moments: The case of smoking cessation. Health Educ Res. 2003;18(2):156-70.
24. Clinical Practice Guidelines Antenatal care – Module 1. Department of Health and Ageing. 2012 [cited 24 June 2013]; Available from: www.health.gov.au
25. Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: US Dept of Health and Human Services, Public Health Service; 2008.
26. Mullen PD, Carbonari JP, Tabak ER, MC. G. Improving disclosure of smoking by pregnant women. Am J Obstet Gynecol 1991;165:409-13.
27. Chamberlain C, O'Mara-Eves A, Oliver S, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev. 2017;10:CD001055.
28. Coleman T, Chamberlain C, Davey MA, Cooper SE, J. L-B. Pharmacological interventions for promoting smoking cessation during pregnancy. 2015. Cochrane Database Syst Rev 2015(12):No. CD010078.
29. Colman GJ, T. J. Trends in smoking before, during, and after pregnancy in ten states. American journal of preventive medicine. 2003;24(1):29-35.

30. Fang WL, Goldstein AO, Butzen AY, al. e. Smoking cessation in pregnancy: A review of postpartum relapse prevention strategies. J Am Board Fam Pract. 2004;17(4):264-75.
31. Hotham E, Ali R WJ, Robinson J. . Pregnancy-related changes in tobacco, alcohol and cannabis use reported by antenatal patients at two public hospitals in south australia. . Aust N Z J Obstet Gynaecol 2008;48(3):248-54.
32. Tong VT EL, Dietz PM, Asare LA. Smoking patterns and use of cessation interventions during pregnancy. American journal of preventive medicine. 2008;35(4):327-33.
33. Lai MC, Chou FS, Yang YJ, Wang CC, Lee MC. Tobacco use and environmental smoke exposure among Taiwanese pregnant smokers and recent quitters: risk perception, attitude, and avoidance behavior. Int J Environ Res Public Health. 2013;10(9):4104-16.
34. Smedberg J LA, Mardby AC, Nordeng H. Characteristics of women who continue smoking during pregnancy: A cross-sectional study of pregnant women and new mothers in 15 european countries. . BMC Pregnancy Childbirth. 2014;14:213-2393-14-213.
35. Ekblad M GM, Korkeila J, Lehtonen L. Trends and risk groups for smoking during pregnancy in finland and other nordic countries. . Eur J Public Health 2014;24(4):544-51.
36. Goodwin RD, Keves K., N. S. Mental disorders and nicotine dependance among pregnant women in the United States. Obstet Gynecol. 2007;109:875-83.
37. WHO. Global status report on noncommunicable diseases 2010. Geneva; 2010.
38. Horta BL KM, Platt RW. . Maternal smoking and the risk of early weaning: A meta-analysis. Am J Public Health. 2001;91(2):304-7.
39. Liu F ML, Yi MJ. . Association of breastfeeding with behavioral problems and temperament development in children aged 4-5 years. Zhongguo Dang Dai Er Ke Za Zhi. 2006;8(4):334-7.
40. Weiser TM LM, Garikapaty V, Feyerharm RW, Bensyl DM, Zhu BP. . Association of maternal smoking status with breastfeeding practices: Missouri, 2005. Pediatrics. 2009;124(6):1603-10.
41. Vohr BR PB, Dusick AM, et al. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. Pediatrics. 2006;118(1):e115-23.
42. Vohr BR PB, Dusick AM, et al. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. Pediatrics. 2007;120(4):e953-9.
43. Nations U. Framework convention on tobacco control of world health organisation. 2003.

REFERENCES

44. Castles A AE, Melvin CL, Kelsch C, Boulton ML. . Effects of smoking during pregnancy. five meta-analyses. American journal of preventive medicine. 1999;16(3):208-15.
45. Ananth C DK, Smulian J, Vintzileos A. . Placenta previa in singleton and twin births in the united states,1989 through 1998:A comparison of risk factor profiles and associated conditions. Am J Obstet Gynecol. 2003;188:275-81.
46. Aliyu MH LO, Wilson RE, et al. . Association between tobacco use in pregnancy and placenta-associated syndromes: A population-based study. Arch Gynecol Obstet. 2011;283(4):729-34.
47. Committee on Environmental HealthHealth CoSA, Committee on Adolescence, Committee on Native American Child. . From the american academy of pediatrics: Policy statement-tobacco use: A pediatric disease. Pediatrics. 2009;124(5):1474-87.
48. Einarson A RS. Smoking in pregnancy and lactation: A review of risks and cessation strategies. . Eur J Clin Pharmacol 2009;65(4):325-30.
49. JM. R. Tobacco and pregnancy. Reprod Toxicol. 2009;28(2):152-60.
50. Eisner MD, Iribarren C, Yelin EH, et al. The impact of SHS exposure on health status and exacerbations among patients with COPD. Int J Chron Obstruct Pulmon Dis. 2009;4:169-76.
51. Chi YW, Jaff MR. Optimal risk factor modification and medical management of the patient with peripheral arterial disease. Catheter Cardiovasc Interv. 2008;71(4):475-89.
52. Barker D OC, Simmonds S, Wield G. . The relation of head size and thinness at birth to death from cardiovascular disease in adult life. BMJ. 1993;306:422-6.
53. Hofhuis W dJJ, Merkus PJ. . Adverse health effects of prenatal and postnatal tobacco smoke exposure on children. Arch Dis Child. 2003;88(12):1086-90.
54. Nations U. Convention of united nations on the rights of child. 1989.
55. USDHHS. Women and smoking A report of the surgeon General. 2001.
56. Gavin N, Wiesen C, Layton C. Review and meta-analysis of the evidence on the impact of smoking on perinatal conditions bull into SAMMECII, final report to the national centre for the chronic disease prevention and health promotion. 2001;RTI Project NO 7171-010.
57. American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome. The changing concept of sudden infant death syndrome: Diagnostic coding shifts, controversies regarding the sleeping environment, and new variables to consider in reducing risk. Pediatrics. 2005;116(5):1245-1255.
58. Stick SM, Burton PR, Gurrin L, Sly PD,

LeSouef PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet. 1996;348(9034):1060-1064.
59. Dezateux C, Stocks J. Lung development and early origins of childhood respiratory illness. Br Med Bull. 1997;53(1):40-57.
60. Hoo AF, Henschen M, Dezateux C, Costeloe K, Stocks J. Respiratory function among preterm infants whose mothers smoked during pregnancy. Am J Respir Crit Care Med. 1998;158(3):700-705.
61. Alati R, Al Mamun A, O'Callaghan M, Najman JM, Williams GM. In utero and postnatal maternal smoking and asthma in adolescence. Epidemiology. 2006;17(2):138-144.
62. Bisgaard H, Dalgaard P, Nyboe J. Risk factors for wheezing during infancy. A study of 5,953 infants. Acta Paediatr Scand. 1987;76(5):719-726.
63. Dombrowski SC, Martin RP, Huttunen MO. Gestational exposure to cigarette smoke imperils the long-term physical and mental health of offspring. Birth Defects Res A Clin Mol Teratol. 2005;73(3):170-176.
64. Browne CA, Colditz PB, Dunster KR. Infant autonomic function is altered by maternal smoking during pregnancy. Early Hum Dev. 2000;59(3):209-218.
65. Olds D. Tobacco exposure and impaired development: A review of the evidence. Ment Retard Dev Disabil Res Rev. 1997;3:257-269.
66. Ananth CV, Cnattingius S. Influence of maternal smoking on placental abruption in successive pregnancies: A population-based prospective cohort study in sweden. Am J Epidemiol. 2007;166(3):289-295.
67. Brennan PA, Grekin ER, Mednick SA. Maternal smoking during pregnancy and adult male criminal outcomes. Arch Gen Psychiatry. 1999;56(3):215-219.
68. Gillberg C, Wing L. Autism: Not an extremely rare disorder. Acta Psychiatr Scand. 1999;99(6):399-406.
69. Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology. 2002;13(4):417-423.
70. Ramlau-Hansen CH, Thulstrup AM, Bonde JP, Olsen J. Parental infertility and semen quality in male offspring: A follow-up study. Am J Epidemiol. 2007;166(5):568-570.
71. Himmelberger DU, Brown BW,Jr, cohen EN. Cigarette smoking during pregnancy and the occurrence of spontaneous abortion and congenital abnormality. Am J Epidemiol. 1978;108(6):470-479.
72. Wisborg K, Henriksen TB, Obel C, Skajaa E, Ostergaard JR. Smoking during pregnancy and hospitalization of the child. Pediatrics. 1999;104(4):e46.
73. Blatt K, Moore E, Chen A, Van Hook J, DeFranco EA. Association of reported trimester-specific smoking cessation with

REFERENCES

fetal growth restriction. Obstet Gynecol. 2015;125(6):1452-1459.

74. Mantziou V, Vardavas CI, Kletsiou E, Priftis KN. Predictors of childhood exposure to parental secondhand smoke in the house and family car. Int J Environ Res Public Health. 2009;6(2):433-444.
75. Martins-Green M, Adhami N, Frankos M, et al. Cigarette smoke toxins deposited on surfaces: Implications for human health. PLoS One. 2014;9(1):e86391.
76. New Zealand Ministry of Health. Background and recommendation of the New Zealand guidelines for helping people to stop smoking: Providing stop-smoking support to pregnant and breastfeeding women. 2014.
77. National Institute for Health and Clinical Excellence (2010) PH26 Quitting smoking in pregnancy and following childbirth. London: NICE. Available www.nice.org.uk/PH26. Reproduced with permission. NICE guidance is prepared for the National Health Service in England and Wales. NICE guidance does not apply to Greece and NICE has not been involved in the development or adaptation of any guidance for use in Greece.
78. McCowan LM, Dekker GA, Chan E, et al. Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: Prospective cohort study. BMJ. 2009;338:b1081.
79. Raisanen S, Sankilampi U, Gissler M, et al. Smoking cessation in the first trimester reduces most obstetric risks, but not the risks of major congenital anomalies and admission to neonatal care: A population-based cohort study of 1,164,953 singleton pregnancies in finland. J Epidemiol Community Health. 2014;68(2):159-164.
80. Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev. 2009;(3):CD001055. doi(3):CD001055.
81. Marks JS, Koplan JP, Hogue CJ, Dalmat ME. A cost-benefit/cost-effectiveness analysis of smoking cessation for pregnant women. Am J Prev Med. 1990;6(5):282-289.
82. Lightwood JM, Phibbs CS, Glantz SA. Short-term health and economic benefits of smoking cessation: Low birth weight. Pediatrics. 1999;104(6):1312-1320.
83. Ayadi MF, Adams EK, Melvin CL, et al. Costs of a smoking cessation counseling intervention for pregnant women: Comparison of three settings. Public Health Rep. 2006;121(2):120-126.
84. Melvin CL, Dolan-Mullen P, Windsor RA, Whiteside HP,Jr, Goldenberg RL. Recommended cessation counselling for pregnant women who smoke: A review of the evidence. Tob Control. 2000;9 Suppl 3:III80-4.
85. Rovina N, Gratziou C. Smoking cessation strategies. Pneumon. 2005;18:245-262.

86. Maxson PJ, Edwards SE, Ingram A, Miranda ML. Psychosocial differences between smokers and non-smokers during pregnancy. Addict Behav. 2012;37(2):153-159.
87. Hauge LJ, Torgersen L, Vollrath M. Associations between maternal stress and smoking: Findings from a population-based prospective cohort study. Addiction. 2012;107(6):1168-1173.
88. Lopez W, Konrath S, Seng J. Abuse-Related Post-Traumatic stress, coping, and tobacco use in pregnancy. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG. 2011:422-432.
89. Burgess DJ, Fu SS, Noorbaloochi S, et al. Employment, gender, and smoking cessation outcomes in low-income smokers using nicotine replacement therapy. Nicotine Tob Res. 2009;11(12):1439-1447.
90. Winickoff JP, Healey EA, Regan S, et al. Using the postpartum hospital stay to address mothers' and fathers' smoking: The NEWS study. Pediatrics. 2010;125(3):518-525.
91. Grimstad H, Backe B, Jacobsen G, Schei B. Abuse history and health risk behaviors in pregnancy. Acta Obstet Gynecol Scand. 1998;77(9):893-897.
92. Morland L, Goebert D, Onoye J, et al. Posttraumatic stress disorder and pregnancy health: Preliminary update and implications. Psychosomatics. 2007;48(4):304-308.
93. Ebert LM, Fahy K. Why do women continue to smoke in pregnancy? Women Birth. 2007;20(4):161-168.
94. Flemming K, Graham H, Heirs M, Fox D, Sowden A. Smoking in pregnancy: A systematic review of qualitative research of women who commence pregnancy as smokers. J Adv Nurs. 2013;69(5):1023-1036.
95. Shih SF, Chen L, Wen CP, Yang WC, Shih YT. An investigation of the smoking behaviours of parents before, during and after the birth of their children in taiwan. BMC Public Health. 2008;8:67-2458-8-67.
96. Penn G, Owen L. Factors associated with continued smoking during pregnancy: Analysis of socio-demographic, pregnancy and smoking-related factors. Drug Alcohol Rev. 2002;21(1):17-25.
97. Eddy DM. David eddy ranks the tests. Harv Health Lett. 1992;17(suppl):10-11.
98. McBride CM, Emmons KM, Lipkus IM. Understanding the potential of teachable moments: The case of smoking cessation. Health Educ Res. 2003;18(2):156-170.
99. Petersen Z, Nilsson M, Everett K, Emmelin M. Possibilities for transparency and trust in the communication between midwives and pregnant women: The case of smoking. Midwifery. 2009;25(4):382-391.
100. Bryce A, Butler C, Gnich W, Sheehy C, Tappin DM. CATCH: Development of a home-based midwifery intervention to support young pregnant smokers to quit. Midwifery.

REFERENCES

2009;25(5):473-482.

101. Flower A, Shawe J, Stephenson J, Doyle P. Pregnancy planning, smoking behaviour during pregnancy, and neonatal outcome: UK millennium cohort study. BMC Pregnancy Childbirth. 2013;13:238-2393-13-238.
102. WHO. WHO report on the global tobacco epidemic, 2009.
103. Sarna L, Bialous SA, Rice VH, Wewers ME. Promoting tobacco dependence treatment in nursing education. Drug Alcohol Rev. 2009;28(5):507-516.
104. Smith DR. Tobacco control and the nursing profession. Nurs Health Sci. 2010;12(1):1-3.
105. Gebauer C, Kwo CY, Haynes EF, Wewers ME. A nurse-managed smoking cessation intervention during pregnancy. J Obstet Gynecol Neonatal Nurs. 1998;27(1):47-53.
106. Gaffney KF, Baghi H, Sheehan SE. Two decades of nurse-led research on smoking during pregnancy and postpartum: Concept development to intervention trials. Annu Rev Nurs Res. 2009;27:195-219.
107. Rice VH, Hartmann-Boyce J, Stead LF. Nursing interventions for smoking cessation. The Cochrane database of systematic reviews. 2013;8:001188.
108. Samet J, Yoon S. Gender, women, and the tobacco epidemic. 2010.
109. Baxter S, Blank L, Guillaume L, Messina J, Everson-Hock E, Burrows J. Systematic review of how to stop smoking in pregnancy and following childbirth. 2009. NICE Report. https://www.nice.org.uk/guidance/ph26/documents/quitting-smoking-in-pregnancy-and-following-childbirth-evidence-review-full-report2
110. Tappin DM, MacAskill S, Bauld L, Eadie D, Shipton D, Galbraith L. Smoking prevalence and smoking cessation services for pregnant women in scotland. Subst Abuse Treat Prev Policy. 2010;5:1-597X-5-1.
111. World Health Organization. WHO report on the global tobacco epidemic, 2009.
112. Lee NL, Samet JM, Yang G, et al. Prenatal secondhand smoke exposure and infant birth weight in china. Int J Environ Res Public Health. 2012;9(10):3398-3420.
113. Webb DA, Boyd NR, Messina D, Windsor RA. The discrepancy between self-reported smoking status and urine continine levels among women enrolled in prenatal care at four publicly funded clinical sites. J Public Health Manag Pract. 2003;9(4):322-325.
114. Hegaard HK, Kjaergaard H, Moller LF, Wachmann H, Ottesen B. Multimodal intervention raises smoking cessation rate during pregnancy. Acta Obstet Gynecol Scand. 2003;82(9):813-819.
115. Acosta M, Buchhalter A, Breland A, Hamilton D, Eissenberg T. Urine cotinine as an index of smoking status in smokers during 96-hr abstinence: Comparison between gas chromatography/mass spectrometry and

immunoassay test strips. Nicotine Tob Res. 2004;6(4):615-620.
116. Binnie V, McHugh S, Macpherson L, Borland B, Moir K, Malik K. The validation of self-reported smoking status by analysing cotinine levels in stimulated and unstimulated saliva, serum and urine. Oral Dis. 2004;10(5):287-293.
117. European Network on Smoking Prevention. European smoking cessation guidelines. 2012.
118. Benowitz N. Cotinine as a biomarker of environmental tobacco smoke exposure. Epidemiol Rev. 1996;18:188-204.
119. Rebagliato M, Bolumar F, Florey Cdu V, et al. Variations in cotinine levels in smokers during and after pregnancy. Am J Obstet Gynecol. 1998;178(3):568-571.
120. Haddow JE, Knight GJ, Palomaki GE, Haddow PK. Estimating fetal morbidity and mortality resulting from cigarette smoke exposure by measuring cotinine levels in maternal serum. Prog Clin Biol Res. 1988;281:289-300.
121. EPA California. Proposed identification of environmental tobacco smoke as a toxic air contaminant. 2004. 2004.
122. Nakahara Y. Hair analysis for abused and therapeutic drugs. J Chromatogr B Biomed Sci Appl. 1999;733(1-2):161-180.
123. Klein J, Blanchette P, Koren G. Assessing nicotine metabolism in pregnancy--a novel approach using hair analysis. Forensic Sci Int. 2004;145(2-3):191-194.
124. Fagerstrom K. How to measure nicotine dependence. In: Wilhelmsen L, ed. Smoking as a cardiovascular risk factor –New strategies for smoking cessation. New York (NY): Hogrefe and Huber Publishers; 1991.
125. Etter JF, Duc TV, Perneger TV. Validity of the fagerstrom test for nicotine dependence and of the heaviness of smoking index among relatively light smokers. Addiction. 1999;94(2):269-281.
126. Pomerleau CS, Pomerleau OF, Majchrzak MJ, Kloska DD, Malakuti R. Relationship between nicotine tolerance questionnaire scores and plasma cotinine. Addict Behav. 1990;15(1):73-80.
127. Berlin I, Singleton EG, Heishman SJ. A comparison of the fagerstrom test for cigarette dependence and cigarette dependence scale in a treatment-seeking sample of pregnant smokers. Nicotine Tob Res. 2016;18(4):477-483.
128. Yang I, Hall LA. Nicotine dependence measures for perinatal women. Clin Nurs Res. 2016.
129. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: Using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. Br J Addict. 1989;84(7):791-799.
130. Abrams D, Niaura R, Brown R, Emmons K, Goldstein M, Monti P. The tobacco treatment

REFERENCES

handbook: A guide to best practices. New York: Guilford Press; 2003.

131. Ortendahl M, Nasman P. Perception of smoking-related health consequences among pregnant and non-pregnant women. Am J Addict. 2007;16(6):521-527.
132. Rigotti NA, Park ER, Regan S, et al. Efficacy of telephone counseling for pregnant smokers: A randomized controlled trial. Obstet Gynecol. 2006;108(1):83-92.
133. Windsor RA, Lowe JB, Perkins LL, et al. Health education for pregnant smokers: Its behavioral impact and cost benefit. Am J Public Health. 1993;83(2):201-206.
134. Walsh RA, Redman S, Brinsmead MW, Byrne JM, Melmeth A. A smoking cessation program at a public antenatal clinic. Am J Public Health. 1997;87(7):1201-1204.
135. Windsor RA, Woodby LL, Miller TM, Hardin JM, Crawford MA, DiClemente CC. Effectiveness of agency for health care policy and research clinical practice guideline and patient education methods for pregnant smokers in medicaid maternity care. Am J Obstet Gynecol. 2000;182(1 Pt 1):68-75.
136. Hajek P, West R, Lee A, et al. Randomized controlled trial of a midwife-delivered brief smoking cessation intervention in pregnancy. Addiction. 2001;96(3):485-494.
137. Hughes EG, Lamont DA, Beecroft ML, Wilson DM, Brennan BG, Rice SC. Randomized trial of a "stage-of-change" oriented smoking cessation intervention in infertile and pregnant women. Fertil Steril. 2000;74(3):498-503.
138. Prochaska J, Norcross J, DiClemente C. Changing for good. New York: William Morrow and Company; 1994.
139. Prochaska JJ, Hall SE, Hall SM. Stage-tailored tobacco cessation treatment in inpatient psychiatry. Psychiatr Serv. 2009;60(6):848.
140. Lawrence T, Aveyard P, Evans O, Cheng KK. A cluster randomised controlled trial of smoking cessation in pregnant women comparing interventions based on the transtheoretical (stages of change) model to standard care. Tob Control. 2003;12(2):168-177.
141. McBride CM, Curry SJ, Grothaus LC, Nelson JC, Lando H, Pirie PL. Partner smoking status and pregnant smoker's perceptions of support for and likelihood of smoking cessation. Health Psychol. 1998;17(1):63-69.
142. Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. Cochrane Database Syst Rev. 2013;8:CD002850.
143. Bombard JM, Farr SL, Dietz PM, Tong VT, Zhang L, Rabius V. Telephone smoking cessation quitline use among pregnant and non-pregnant women. Matern Child Health J. 2013;17(6):989-995.
144. Boldemann C, Gilljam H, Lund KE, Helgason AR. Smoking cessation in general practice:

The effects of a quitline. Nicotine and Tobacco Research. 2006;8(6):785-790.
145. Cummins S, Zhu S, Tedeschi G, et al. Proactive recruitment of pregnant smokers into cessation services through the healthcare setting. Nicotine Tob Res. 2002;4:363-383.
146. Higgins ST, Bernstein IM, Washio Y, et al. Effects of smoking cessation with voucher-based contingency management on birth outcomes. Addiction. 2010;105(11):2023-2030.
147. Donatelle RJ, Prows SL, Champeau D, Hudson D. Randomised controlled trial using social support and financial incentives for high risk pregnant smokers: Significant other supporter (SOS) program. Tob Control. 2000;9 Suppl 3:III67-9.
148. Lawrence T, Aveyard P, Croghan E. What happens to women's self-reported cigarette consumption and urinary cotinine levels in pregnancy?. Addiction. 2003;98(9):1315-1320.
149. Hartmann-Boyce J, Lancaster T, Stead LF. Print-based self-help interventions for smoking cessation. Cochrane Database Syst Rev. 2014;6:CD001118.
150. Strecher V. The internet: Just another smoking cessation tool? Addiction. 2008(103):485-486.
151. Butterworth S, Sparkes E, Trout A, Brown K. Pregnant smokers' perceptions of specialist smoking cessation services. J. Smok. Cessat. 2014;9(2):85-89.
152. Tombor I, Neale J, Shahab L, Ruiz M, West R. Healthcare providers' views on digital smoking cessation interventions for pregnant women. Jounral Smoking Cessation. 2014.
153. Heil SH, Linares Scott T, Higgins ST. An overview of principles of effective treatment of substance use disorders and their potential application to pregnant cigarette smokers. Drug Alcohol Depend. 2009;104 Suppl 1:S106-14.
154. Herbec A, Brown J, Tombor I, Michie S, West R. Pilot randomized controlled trial of an internet-based smoking cessation intervention for pregnant smokers ('MumsQuit'). Drug Alcohol Depend. 2014;140:130-136.
155. Civljak M, Stead LF, Hartmann-Boyce J, Sheikh A, Car J. Internet-based interventions for smoking cessation. Cochrane Database Syst Rev. 2013;7:CD007078.
156. McBride CM, Pirie PL, Curry SJ. Postpartum relapse to smoking: A prospective study. Health Educ Res. 1992;7(3):381-390.
157. Ratner PA, Johnson JL, Bottorff JL, Dahinten S, Hall W. Twelve-month follow-up of a smoking relapse prevention intervention for postpartum women. Addict Behav. 2000;25(1):81-92.
158. Edwards N, Sims-Jones N. Smoking and smoking relapse during pregnancy and postpartum: Results of a qualitative study. Birth. 1998;25(2):94-100.
159. Tong VT, Dietz PM, Rolle IV, Kennedy SM,

REFERENCES

Thomas W, England LJ. Clinical interventions to reduce secondhand smoke exposure among pregnant women: A systematic review. Tob Control. 2015;24(3):217-223.

160. Blaakman SW, Borrelli B, Wiesenthal EN, et al. Secondhand smoke exposure reduction after NICU discharge: Results of a randomized trial. Acad Pediatr. 2015;15(6):605-612.
161. Hawkins SS, Baum CF, Oken E, Gillman MW. Associations of tobacco control policies with birth outcomes. JAMA Pediatr. 2014;168(11):e142365.
162. Been JV, Sheikh A. Investigating the link between smoke-free legislation and stillbirths. Expert Rev Respir Med. 2016;10(2):109-112.
163. Dhalwani NN, Szatkowski L, Coleman T, Fiaschi L, Tata LJ. Nicotine replacement therapy in pregnancy and major congenital anomalies in offspring. Pediatrics. 2015;135(5):859-867.
164. Fiore MC, Jaén CR, Baker TB, et al. Treating tobacco use and dependence: 2008 update. Clinical practice guideline. . 2008.
165. U.S. Preventive Services Task Force. Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: U.S. preventive services task force reaffirmation recommendation statement. Ann Intern Med. 2009;150(8):551-555.
166. Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. Drug Saf. 2001;24(4):277-322.
167. Petersen R, Garrett JM, Melvin CL, Hartmann KE. Medicaid reimbursement for prenatal smoking intervention influences quitting and cessation. Tob Control. 2006;15(1):30-34.
168. Coleman T, Lewis S, Hubbard R, Smith C. Impact of contractual financial incentives on the ascertainment and management of smoking in primary care. Addiction. 2007;102(5):803-808.
169. CAN-ADAPTT. CAN-ADAPTT canadian smoking cessation guideline version 2.0: Specific populations: Pregnant and breastfeeding women. 2011.
170. GlaxoSmithKline. The bupropion pregnancy registry. final report. 2008.
171. Stotts AL, Northrup TF, Cinciripini PM, et al. Randomized, controlled pilot trial of bupropion for pregnant smokers: Challenges and future directions. Am J Perinatol. 2015;32(4):351-356.
172. Chan B, Einarson A, Koren G. Effectiveness of bupropion for smoking cessation during pregnancy. J Addict Dis. 2005;24(2):19-23.
173. Chun-Fai-Chan B, Koren G, Fayez I, et al. Pregnancy outcome of women exposed to bupropion during pregnancy: A prospective comparative study. Am J Obstet Gynecol. 2005;192(3):932-936.
174. Kranzler H. Placebo-controlled trial of bupropion for smoking cessation in pregnant

women (BIBS). . 2014;ClinicalTrials.gov Identifier: NCT02188459 ongoing study.
175. Hankins G. Bupropion for smoking cessation during pregnancy. ClinicalTrials.gov. Accessed March 2016.
176. Pfizer. Varenicline pregnancy cohort study clinical trials. gov identifier:NCT01290445 ongoing study. 2016.
177. Pfizer Canada Inc., ed. Varenicline product monograph; 2011.
178. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.
179. Matt GE QP, Destaillats H, et al. . Thirdhand tobacco smoke: Emerging evidence and arguments for a multidisciplinary research agenda. Environ Health Perspect. 2011;119(9):1218-26.
180. Ferrante G SM, Cibella F, et al. Third-hand smoke exposure and health hazards in children. . Monaldi Arch Chest Dis. 2013;79(1):38-43.
181. Ramirez N OM, Lewis AC, Marce RM, Borrull F, Hamilton JF. . Exposure to nitrosamines in thirdhand tobacco smoke increases cancer risk in non-smokers. Environ Int. 2014;71:139-47.
182. "The 5 A's Model for treating tobacco Use and dependence." In: Treating Tobacco Use and Dependence—2008 Update. October 2014. Agency for Healthcare Research and Quality, Rockville, MD.(for the United States Public Health Service). [cited; Available from: http://www.ncbi.nlm.nih.gov/books/NBK63952/
183. Miyazaki Y HK, Imazeki S. . Smoking cessation in pregnancy: Psychosocial interventions and patient-focused perspectives. Int J Womens Health. 2015;7:415-27.
184. Oncken C DE, Greene J, et al. . Nicotine gum for pregnant smokers: A randomized controlled trial. Obstet Gynecol. 2008;112(4):859-67.
185. Wisborg K HT, Jespersen LB, Secher NJ. . Nicotine patches for pregnant smokers: A randomized controlled study. Obstet Gynecol. 2000;96(6):967-71.
186. The American Congress of Obstetricians and Gynecologists(ACOG). Smoking Cessation During Pregnancy. 2010 [cited 2017; Available from: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/Smoking-Cessation-During-Pregnancy. ■

2.
SMOKING CESSATION AMONG ADOLESCENTS

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About this Guideline

This special chapter of the European Tobacco Treatment Guideline is intended to summarize evidence regarding effective approaches for supporting cessation among adolescents defined broadly as school-aged children between the ages of 10 and 18. This chapter provides a synopsis of existing evidence generated from a systematic review of literature published between 2000-2016 pertaining to adolescent tobacco cessation treatments and describes the effectiveness of various cessation interventions among adolescent smokers in different settings including: health care settings, schools, information and computer technology, and community. Intervention approaches covered in each setting include: behavioural, pharmacological, and combined intervention approaches. It is important to note that this chapter does not address the prevention of the initiation of tobacco use among adolescents but rather on cessation.

Evidence-based recommendations are presented for professionals involved in the delivery of tobacco-related services to adolescents including health care professionals, educators, specialized smoking prevention interventionists and governments. The GRADE evidence grading system has been used to rate the quality of evidence supporting each recommendation. GRADE is a widely accepted tool, which has been endorsed by WHO and other international health care organizations. GRADE uses 4 evidence grading categories: 'high', 'moderate', 'low', 'very low' (see table below). The level of evidence grading appears in brackets at the end of each recommendation statement. Authors acknowledge that in many cases randomized controlled trials are not feasible or necessary for generating high quality evidence in particular in the case of policy based interventions. Evidence grading presented in this chapter reflects this understanding and a careful examination of the evidence.

GRADE - Evidence Grading Categories:

CODE	QUALITY OF EVIDENCE	DEFINITION
A	High	– Further research is very unlikely to change our confidence in the estimate of effect. – Several high-quality studies with consistent results. – In special cases: one large, high-quality multi-center trial
B	Moderate	– Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. – One high-quality study. – Several studies with some limitations.

CODE	QUALITY OF EVIDENCE	DEFINITION
C	Low	– Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. – One or more studies with severe limitations.
D	Very Low	– Any estimate of effect is very uncertain. – Expert opinion. – No direct research evidence. – One or more studies with very severe limitations.

EXECUTIVE SUMMARY

SMOKING CESSATION AMONG ADOLESCENTS

Experimentation with tobacco is common during adolescence.[1] More than half of European students reported experimenting with tobacco use and an estimated 21% of 16-year-old students in Europe are current smokers (i.e. smoked in the past 30 days).[2] The use of electronic cigarettes has also become increasingly popular among adolescents in Europe with 23% of adolescents aged 15-17 years reporting having used, a nicotine containing electronic cigarette and 8% reporting use of non-nicotine containing.[3]

Nicotine dependence develops quickly during adolescence and a large proportion of adolescents who smoke regularly will go on to smoke during adulthood.[4, 5] As such the early identification and treatment of adolescent tobacco use is crucial in preventing more serious short- or longer-term health consequences. There is significant concern that electronic cigarette use could increase progression to daily smoking and undermine cessation efforts.[6]

Smoking Cessation in Adolescent Tobacco Users

A variety of personal, environmental and social factors appear to contribute to cessation outcomes during adolescence (see table). For example, adolescent tobacco users with a higher daily cigarette consumption as well as alcohol consumption are less likely to quit smoking.[7, 8] Having friends who smoke is also associated with poorer cessation outcomes.[9, 10]

Factors which affect adolsecents likelihood of quitting smoking

LESS LIKELY TO GUIT	MORE LIKELY TO QUIT
Females	– Males
Greater Nioctine Addiction	– Older Age
Drug or Alcohol Use	– Hight motivation to quit
Peer Tobacco Use (Friends who smoke)	– Academic Success
Family (Parent and sibling) Tobacco Use	– Slow Nicotine Metabolizer
Mental Health Illness	
Overweight	
Physical inactivity	
Family Stress	

Source: Adapted from Harvey & Chadi, 2016.[11]

Tobacco Treatment Interventions in Adolescent Tobacco Users.

Although an increasing number of trials have been conducted during the past decade, identifying effective interventions for adolescent smoking cessation is still extremely difficult.[12-14] There is substantial variability among intervention strategies tested to date making the identification of high quality evidence challenging.[11, 13, 15, 16]

It is recognized that adolescent tobacco users are a unique population and require tailored approaches to support smoking cessation.[17] Health care professionals and educators working with adolescents should be aware of the needs and preferences of adolescent tobacco users.[18] Cessation messages should be tailored to the specific beliefs, interest and characteristics of adolescents in order to be most persuasive.[19] For example research has found students rate "long-term health effects", "impaired sports performance" and "decreased attractiveness" as the most important reasons to quit smoking.[19] Short-term effects of smoking appear more persuasive than longer-term effects.[19]

Counselling

There is good evidence that counselling is the most effective cessation intervention for adolescent tobacco users.[11, 13, 15, 16] Counselling strategies have been shown to reduce daily cigarette consumption short-term abstinence among adolescents and, and there is some evidence to indicate that counselling may increase the likelihood of long term smoking abstinence.[11, 13, 15] The counseling interventions with the strongest level of evidence to support them are those which employed motivational enhancement, stage matched interventions, and cognitive behavioural therapy (CBT).[11, 13-15, 17]

Pharmacotherapy

There have been very few trials to examined quit smoking pharmacotherapies in adolescent populations.[13]

Nicotine Replacement Therapy (NRT) is safe for use in adolescent populations with adverse health effects being include local skin irritation, headache,[20-22] nausea/vomiting, [21, 23] tiredness, sleep disturbances, joint/muscle ache,[24-26] and light headedness/dizziness.[13]

There is some evidence to indicate NRTs are effective in reducing cigarettes smoked per day, but there is a lack of clear evidence regarding the efficacy of NRTs in supporting long-term smoking abstinence among adolescent tobacco users.[13, 20, 21, 24-26] As such NRT is recommended as a second-line therapy for use among daily adolescent tobacco users who are dependant on nicotine. NRT is not recommended for occasional adolescent tobacco users. It is recommended that NRT be used in combination with counselling to maximize cessation outcomes.

There is insufficient evidence at this time to recommend the use of Bupropion and Varenicline for smoking cessation in adolescent populations.[13] More research is required to strengthen the evidence to support recommendations regarding the use of pharmacotherapy among adolescent tobacco users.[13]

Health Care Settings

In Europe, two-thirds of children and adolescents aged 8–18 years will visit a health care professional at least once a year, with a mean number of visits being 2.5.[27] Health care settings (primary care, secondary care, dentists) offer important opportunities for delivering cessation interventions that target adolescent smokers.[16]

Health care professionals have a very important role in terms of preventing tobacco use and supporting cessation among adolescents. The '5 A's' (Ask-Advise-Assess-Assist-Arrange) model is the recommended framework for delivering cessation treatment in clinical settings including intervening with adolescents (see figure).[28, 29] Specifically, health care professionals should document tobacco and electronic cigarette use among all adolescents. Clinicians should provide brief cessation advice and assistance with quitting which includes counselling and pharmacotherapy as appropriate to all adolescents reporting tobacco or electronic cigarette use.[15 16]

School-based Interventions

School-based interventions have several advantages including high rates of access to adolescent populations. There is also evidence to suggest that school settings are preferred by adolescent tobacco users compared to health care or other settings for receiving cessation support.[30]

Meta-analysis data has shown that adolescent tobacco cessation programs are more likely to be effective if they are offered within the school setting.[31] Specifically motivational enhancement intervention programs and those employing cognitive behavioural techniques, delivered in schools over an extended period of time and include multiple components have been found to be effective in supporting short-term smoking cessation and smoking reduction.[13, 31] Length of intervention appears to be an important predictor of successful smoking cessation outcomes with higher cessation rates found for programs lasting for at least five sessions.[31, 32] 'Project EX' (www.projectex.usc.edu), and the 'Not on Tobacco -NOT' (www.lung.org/associations/states/colorado/tobacco/not-on-tobacco) are two group-based school-based smoking cessation programs for adolescents which are promising international best practices.[13, 33-35]

Information Technology

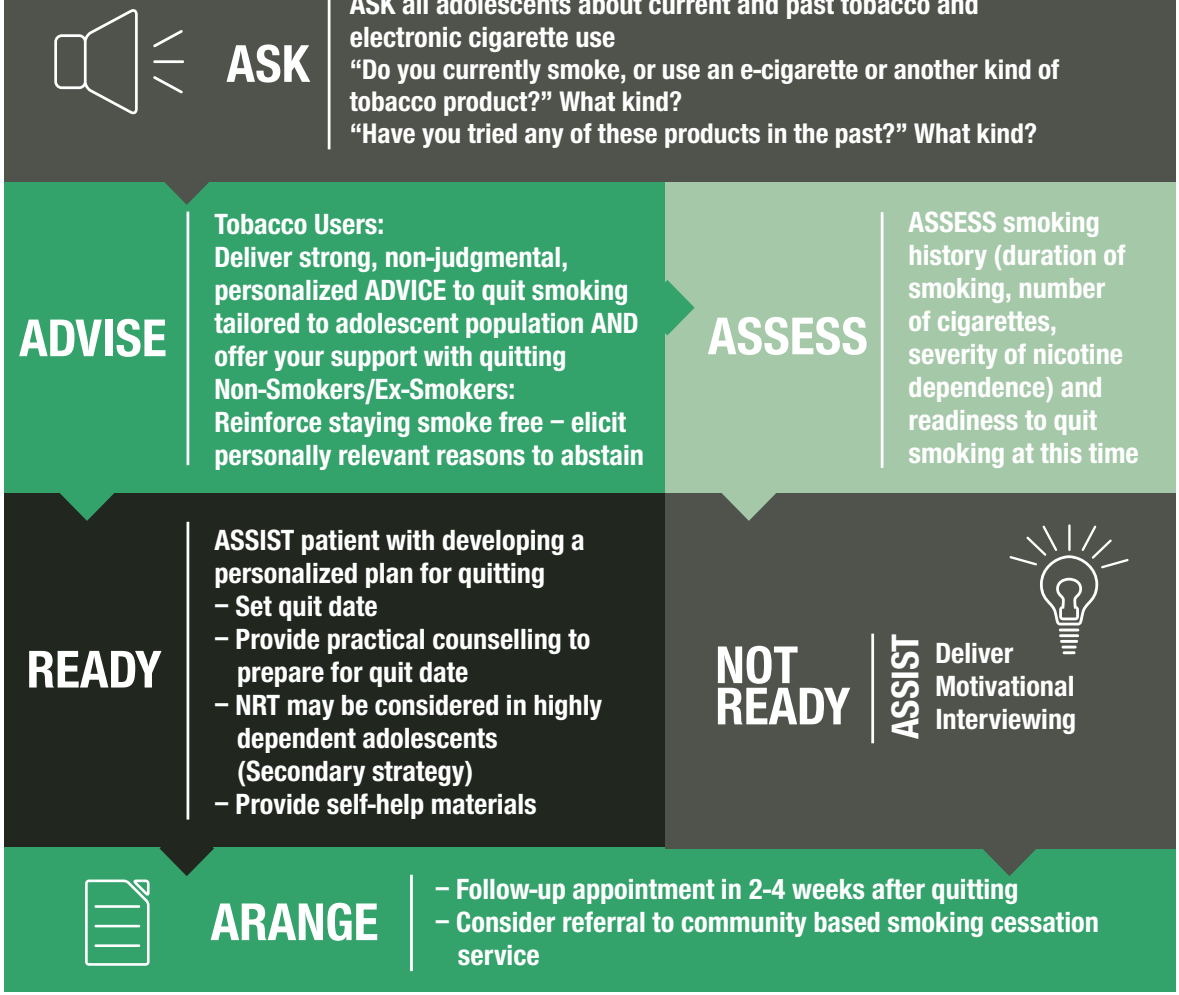
There has been increased interest in the use of technology to intervene with adolescent tobacco users. In particular

interventions using text messages, digital self-help materials, and other technology-based applications have been tested in the literature. While these are promising strategies, data supporting the effectiveness of technology-based interventions is limited and as such it is recommended that they be used in combination with counselling.[13, 17, 36-38]

Policy-based Interventions

At the municipality, country, or EU-level, legislative and policy efforts can contribute to supporting smoking cessation in adolescence. Increasing the price of cigarettes is particularly effective on adolescents and young people and is correlated to lower smoking initiation for non-smokers, and quitting or reducing smoking for smokers.[39-42] There is some evidence that exposure to cigarette advertising is associated with a higher likelihood of adolescents initiating or continuing tobacco use.[43] Likewise there is evidence, indicating that restrictions and bans on the sale of tobacco to children and– adolescents has reduced smoking and cigarette consumption in this age group.[44]

TOBACCO TREATMENT PROTOCOL – ADOLESCENTS



Key Recommendations for Health Professionals:

We summarize here evidence-based recommendations for supporting cessation among adolescent tobacco users.

Policy:

- Increasing the price of cigarettes is a particularly effective for reducing smoking initiation, and quitting or reducing smoking among adolescent tobacco users and should be a employed by all governments as a priority (Level of Evidence A/B).
- Exposure to cigarette advertising is associated with higher likelihood of adolescents initiating or continuing tobacco use. Governments should as such ban tobacco advertising as a priority (Level of Evidence B).
- Governments/health ministries should restrict the sale of tobacco to children and adolescents in order to reduce smoking and cigarette consumption in this age group (Level of Evidence B).

Counselling

- There is good evidence that counselling is the most effective cessation intervention for adolescent tobacco users (Level of Evidence A).
- The counseling interventions with the strongest level of evidence to support them are motivational enhancement and cognitive behavioural therapy (CBT) (Level of Evidence B).

Pharmacotherapy

- Nicotine Replacement Therapy (NRT) is recommended as a second-line therapy for daily adolescent tobacco users who are dependent on nicotine (Level of Evidence B).
- It is recommended that NRT be used in combination with counselling to maximize cessation outcomes (Level of Evidence A).
- There is insufficient evidence to recommend the use of Bupropion and Varenicline for smoking cessation in adolescent populations (Level of Evidence C).

Alternative Therapies

- Acupuncture is not a recommended treatment for smoking cessation among adolescents within health care/medical settings (Level of Evidence C).

Health Care Settings:

- Health care providers should ask all adolescent patients about both tobacco use and electronic cigarette use (Strength of Evidence A).

- Current tobacco users should be counselled about quitting smoking and referred to evidence-based resources to support cessation when indicated (Strength of Evidence B).
- Health care professionals should tailor advice to quit smoking to adolescent tobacco users by focussing on the short and long-term health effects, personal hygiene (smell, bad breath), implications for athletic performance, attractiveness, and the cost of tobacco use in the short and long-term (Strength of Evidence C).
- Health care providers should receive smoking cessation training to increase skill in addressing adolescent tobacco users among tobacco users (Strength of Evidence A).
- Motivational Interviewing delivered by clinicians has been shown to be effective in reducing daily tobacco use among adolescents and as such is a recommended intervention strategy (Level of Evidence B).

School Settings

- School-based smoking cessation interventions that are based on cognitive behavioural or motivational enhancement strategies and are delivered over any extended period of time are effective in decreasing daily tobacco consumption and increasing short-term smoking abstinence and should be offered in all school settings (Level of Evidence B).
- There is some evidence that complex interventions which combine intervention approaches (such as school based group counselling with telephone or mobile phone follow-up support, or incentives) may increase abstinence rates up to a 4-months after treatment as well as reductions in cigarettes smoked per day and are recommended as promising practices for intervening with adolescent tobacco users (Level of Evidence C).

Information Communication Technology

- Information communication technology (ICT) interventions are an effective strategy for decreasing daily tobacco use in adolescents, however available evidence cannot support the use of ICT in supporting long-term smoking cessation;, as such it is recommended information technology interventions be used in combination with other counselling based intervention strategies (Level of Evidence B).

Community Settings

- Community settings, such as summer camps or neighbourhood recreation centres, should be considered for the implementation of smoking cessation interventions in adolescents (Level of Evidence C).

1.0
INTRODUCTION

1.1 Tobacco use in adolescence

Experimentation with tobacco is common during adolescence with almost half of European adolescents reporting experimenting with tobacco use.[2] There has been a significant decline in rates of adolescent use over the years (**Figure 1** and **2**). In 2015, an estimated 21% of 16-year-old students (Grade 10) in Europe were current smokers (i.e. smoked in the past 30 days), and 13% smoked daily,[2] a rate which is significantly higher compared to rates of adolescent smoking in the United States (US) for the same year (12% and 6%, respectively).[45] The highest rates were found in Italy (37 %), Bulgaria and Croatia (33 % each).[2] **Figure 3** provides country specific rates of adolescent tobacco use in 25 EU countries.

FIGURE 1: Cigarette use in the last 30 days by gender 25 country trend 1995-2015 (percentage)

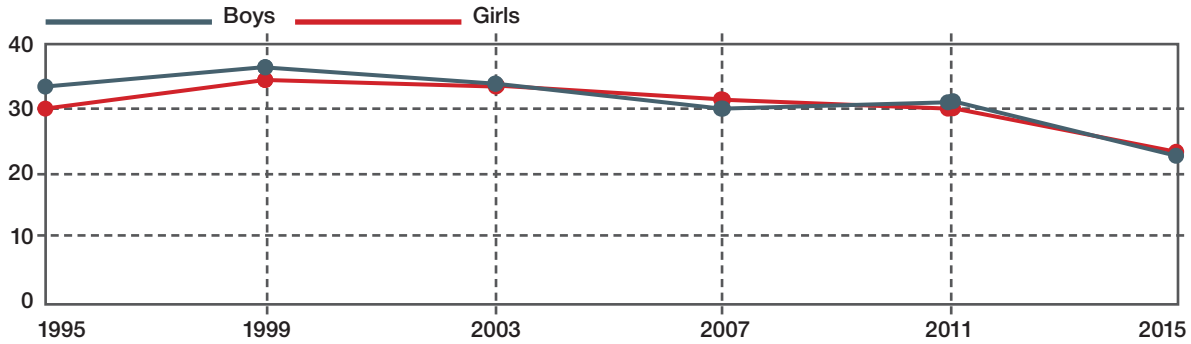
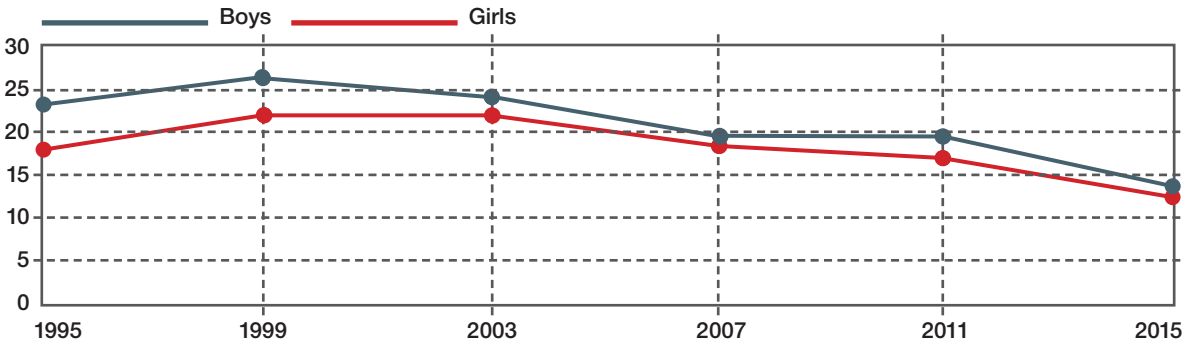


FIGURE 2: Daily cigarette use by gender 25 EU country trend 1995-2015 (percentage)



Source: ESPAD Report 2015.[2]

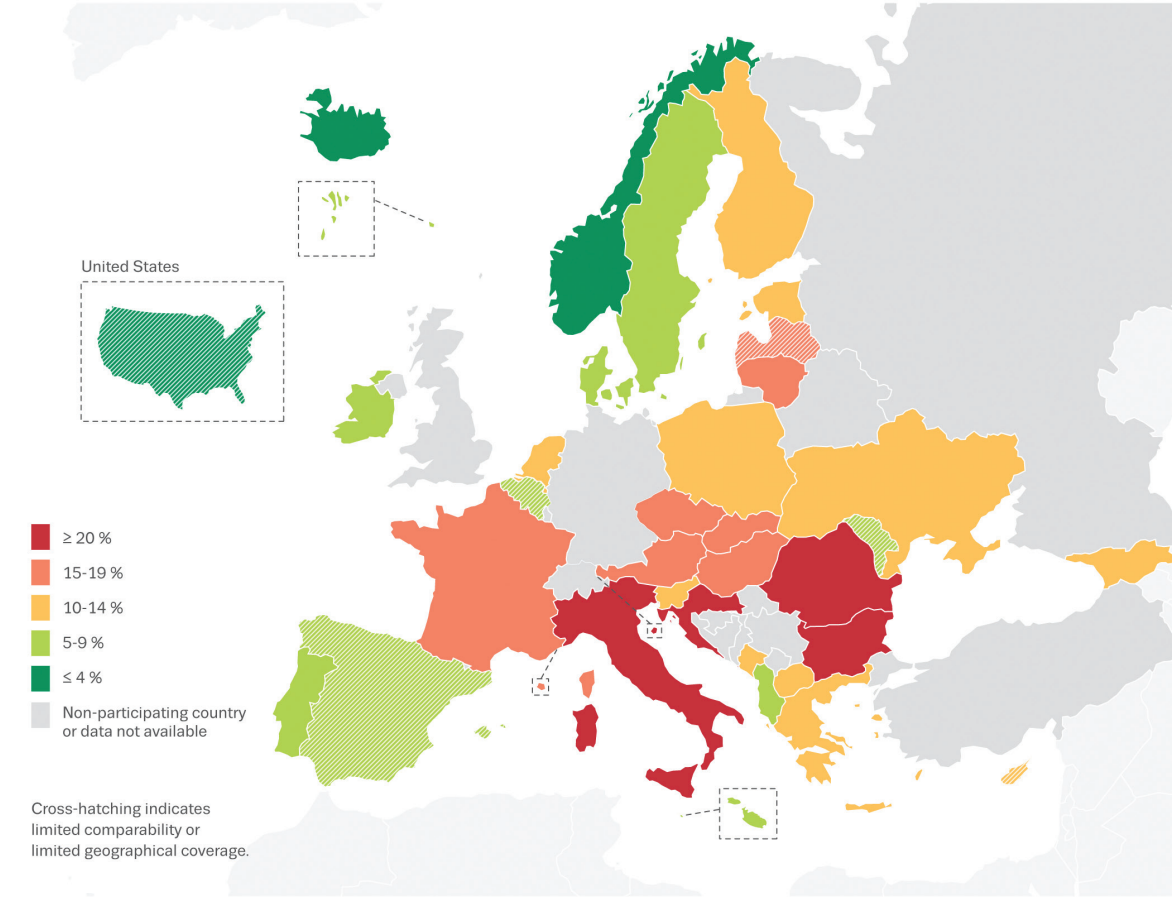
The use of electronic cigarettes has also become increasingly popular among adolescents in Europe with 23% of adolescents aged 15-17 years reporting having used, a nicotine containing electronic cigarette and 8% reporting use of non-nicotine containing.[3] There is significant concern that electronic cigarette use could increase progression to daily smoking and undermine cessation efforts.[6]

Nicotine dependence begins and develops quickly during adolescence,[4] and as such early initiation of tobacco use predicts smoking during adulthood.[12] Two in every three adult smokers in the United Kingdom (UK) smoked their first cigarette before age 18; one in every three started before age 16.[46]

Adolescent smokers experience reduced physical fitness, shortness of breath, higher rates of cough and other respiratory symptoms, addiction to nicotine, and poorer overall health.[1] Adolescent smokers are also more likely to have seen a doctor or other health professionals for an emotional or psychological complaint than non-smokers and to have used other drugs.[47] In the longer term, adolescent smokers have increased risk for impaired lung growth and decreased lung function.[1]

Adolescents have in recent years been increasingly exposed to messages that inform them about the short- and long-term adverse health and social effects of smoking. In 2015, more than 75% of high school seniors in the US thought smoking a pack or more a day was harmful, compared to about 50% in 1975.[45] Adolescent smokers are less cognisant about the addictive nature of tobacco use and studies show that many adolescent smokers do not consider themselves addicted and reported that addiction may apply to adult smokers.[48]

FIGURE 3: Daily tobacco use (past 30-days) by European country



Source: ESPAD Report 2015.[2]

1.2 Intention to quit and rates of smoking cessation in adolescent smokers

A large proportion of adolescent smokers report an interest in quitting. In the 2012 US National Youth Tobacco Survey (NYTS), one in two current youth tobacco users (53%) responded that they intend to quit smoking.[49] An estimated 62% of adolescents identifying as monthly smokers at baseline in a Swiss longitudinal study reported at least one quit attempt in a two year follow-up (mostly unassisted self-quitting); among them one third reported successful quitting.[50]

Adolescence (ages 10–18 years) is a key period for early intervention for both the prevention of tobacco use and support of smoking cessation. Importantly, early identification and treatment of adolescent tobacco use is crucial in preventing more serious short- or longer-term health consequences.

1.3 Existing Guidelines and Recommendations

Several previous guidelines have addressed smoking cessation in adolescent populations[28, 29, 51-57] and were referenced in the preparation of this chapter. **Appendix A** presents a summary of existing guideline recommendations regarding smoking cessation in adolescents and youth.

2.0
FACTORS INFLUENCING ADOLESCENT SMOKING CESSATION

2.1 Individual-level factors

Regardless of the type of intervention provided, smoking cessation is strongly associated with an adolescent's willingness and motivation to quit.[58] A meta-analysis of an US Project-EX-based smoking cessation trial among continuation school students found motivation to quit to be an important predictor of increased cessation rates.[59]

In a number of studies, smoking-related variables which consistently predicted adolescent cessation were lower levels of nicotine dependence (e.g. number of cigarettes smoked per day[7, 8]) and lower rates of alcohol consumption.[60] Slow nicotine metabolism (i.e. CYP2A6 activity) is associated with a higher probability of quitting.[61] Data from six European countries indicated that low nicotine dependence was the most significant predictor of smoking cessation.[62]

It has also been suggested that frequency of smoking,[63] being overweight,[64] physical inactivity[64] and poor academic performance[65] are associated with a lower likelihood of successful quitting. However, one study has indicated that physical activity was positively correlated only with smoking reduction, but not with smoking cessation.[66]

2.2 Role of Peers and Environmental Factors

Empirical research has identified that having friends who smoke is negatively associated with quitting smoking[9, 10] and intentions to quit.[62, 67] Data from studies conducted in Europe confirmed that adolescent smokers experienced greater social influence towards smoking compared to individuals who reported having quit.[62] More specifically, current smokers experienced more pressure to smoke, more smokers in their environment, and both social norms and more positive attitudes toward smoking compared to adolescents who reported having quit smoking.[62] Parental and/or sibling smoking, family stress are also associated with a lower likelihood of quitting.[15, 65]

Although the relationship between social influence and smoking in adolescence appears to be strong, it is noteworthy that this relationship is not consistent across all studies; this is indicative of the complexity of the pathways functioning in adolescent smoking initiation and cessation highlighting the need for extensive as well as current research in adolescent populations from different backgrounds in order to monitor these trends.[68-70] **Table 1** providers a summary of known factors which influence the liklihood that an adolecent will qutt smoking.

TABLE 1: Factors which affect adolsecents likelihood of quitting smoking

LESS LIKELY TO GUIT	MORE LIKELY TO QUIT
Females	– Males
Greater Nioctine Addiction	– Older Age
Drug or Alcohol Use	– Hight motivation to quit
Peer Tobacco Use (Friends who smoke)	– Academic Success
Family (Parent and sibling) Tobacco Use	– Slow Nicotine Metabolizer
Mental Health Illness	
Overweight	
Physical inactivity	
Family Stress	

Source: Adapted from Harvey & Chadi 2016.[11]

3.0
INTERVENING WITH ADOLESCENT TOBACCO USERS

Although an increasing number of trials have been conducted during the past decade, identifying effective interventions for adolescent smoking cessation is still extremely difficult.[12-14] There is substantial variability among intervention strategies tested, samples are often very diverse -both in individual as well as smoking-related characteristics-, recruitment is challenging and low retention rates hinder the evaluation of the implemented programs.[11, 13, 15, 16, 70, 71] Despite these limitations existing experience has provided insight into the design of smoking cessation interventions for adolescents which we summarize in brief here.

3.1 TAILORING INTERVENTIONS

It is recognized that adolescent tobacco users are a unique population and require tailored approaches to support smoking cessation.[17] Health care professionals and educators working with adolescents should be aware of the needs and preferences of adolescent tobacco users.[18]

In a recent literature review by Gabble and colleagues (2015) various strategies to optimize adolescent-targeted intervention designs and messaging were examined.[17] Authors noted that youth cessation intervention should account for factors such as accessibility. Latimer et al. conducted a formative evaluation of various smoking cessation messages, in order to identify the optimal content and presentation approach for this age group; then, on the basis of this evaluation, they created smoking cessation videos and tested their appeal on adolescent high school students.[19] The results of the evaluation confirmed that "message targeting" should build upon the specific beliefs, interests and characteristics of adolescent tobacco users in order to be highly persuasive and effective. Students rated "long-term health effects", "impaired sports performance" and "decreased attractiveness" as the most important reasons to quit smoking. Similarly, according to another study of high school students' smoking behaviours and perceptions about the long-term physiological and pathological effects of smoking had the potential to improve quit rates.[72] This study found adolescents were indifferent about messages that have been used in multiple successful youth tobacco prevention campaigns which focus "concerns on not being accepted by peers" and "being exploited by the tobacco industry".

Table 2 provides a summary of the recommended methods for tailoring cessation messages for adolescent tobacco users.

TABLE 2: Cessation advice for adolescents

FACTORS	DESCRIPTION
Personal Hygiene	– Focuses on factors such as bad smell and bad breath
Decreased Attractiveness	– Focuses on decreased attractiveness to opposite / same sex including likes and dislikes of others, early aging, etc.
Impaired Athletic performance	– Focuses on reduced athletic performance associated with tobacco use
Short term health effects	– Shortness of breath, frequent respiratory illness (e.g. bronchitis, cough), dental problems
Long term health effects	– Reduced long term illness (heart disease, stroke, cancer etc.)
Cost	– Focuses on the short and long term financial cost of tobacco use.

Source: Adapted based on Latimer et al. 2012[19] and Milton et al, 2004[18]

Regarding the "sources" of cessation-related messages, adolescents seemed to prefer messages delivered by adolescents (both current smokers and quitters) as well as athletes and celebrities- teachers, parents, non-smokers and health care professionals were ranked significantly lower in adolescents' preferences as "models" for delivering smoking cessation messages.[19] In another recent study, adolescents indicated a preference for modern formats, such as web and video, with the delivery and tone being "informative but not preachy".[73] One study found when given two similar videos on smoking cessation, one focusing on the "gains" related to smoking cessation while the other focusing on the "losses" related to smoking, adolescents were more receptive to gain-based messages they considered these to be more novel.[19] Given the wide use of loss-framed messages, for instance on warning labels on cigarette packages, the novelty of gain-framed messaging should be taken into consideration.

Based on the results of a formative evaluation, Latimer and associates (2012) reported that in order be more appealing to adolescents, three factors need to be considered for messaging related to smoking cessation programs: message content, presentation approach and framing. Many of the current messages addressing smoking are either unfocused (i.e., they aim to promote both smoking prevention and cessation in the form of generic anti-smoking campaigns), or irrelevant and uninteresting to adolescents (e.g., generic warning labels on cigarette packages).[19] Moreover, according to Lane et al. (2011) adolescent smokers do not appear to be attracted to "traditional" evidence-based cessation interventions such as quit lines and advice delivered by health professionals. A study by Sussman and Sun (2009) suggests that intervention content should be fun and interesting, employing dramatizations, games and other interactive activities.

3.2 POLICY-BASED INTERVENTIONS

At the municipality, country, or EU-level, legislative and policy efforts can contribute to supporting smoking cessation in adolescence. Beginning in the mid-1980s, policies supporting tobacco control have been legislated and implemented in many EU countries, spearheaded by the initiatives of the World Health Organization.[75] Tobacco control policies, such as high taxation of tobacco, bans on public smoking and mass media campaigns, as well as efforts to make smoking less socially acceptable (i.e. denormalization) have widely contributed to overall decline of adult smoking in many countries.[76, 77] Similar, though not as striking, findings regarding the impact of anti-smoking policies have been reported for adolescent smoking as well.[78, 79]

In 1999, the World Bank described the most effective tobacco control policies.[80] The recommended cost-effective anti-smoking initiatives included tobacco price increases, tobacco advertisement bans, health warnings on cigarette packages, restrictions or total bans on smoking in public places, consumer's information and treatments to quit available to everyone.

Increasing the price of cigarettes has been shown to be particularly effective in adolescents and young people.[39, 41, 42] In a study conducted in 87 countries, higher cigarette prices were correlated to lower smoking initiation for non-smokers, and quitting or reducing smoking for smokers.[40] Accordingly, cigarette promotions employing price reductions had an effect on transitioning from experimentation with cigarettes to regular smoking in young people.[81]

In a study by Hublet and associates (2009) multi-level analyses were performed to investigate the associations between well-established, cost-effective tobacco control policies at country level, in 29 different European countries, and smoking prevalence among 15-year-old adolescents. The results yielded significant gender differences in the potential efficacy of smoking policies; in the final model for boys, country-level affluence and the legality of vending machines were significantly associated with regular smoking and price policy was found to be marginally significant. Interestingly, the model for girls found only the legality of vending machines to be marginal-

ly correlated with smoking. Gender differences in the potential influence of smoking policies were also reported on Pförtner 's et al. (2016) study evaluating the association of adolescent smoking with the level of implementation of tobacco control policies, taking into account differences in adolescents' family affluence. For boys, tobacco price was negatively associated with weekly smoking, regardless of their family affluence. For girls, there were socio-economic differences in the association of tobacco control spending with weekly smoking. However, for girls, regardless of their socioeconomic status, no policy was associated with smoking. The study showed that adolescent smoking is strongly influenced by countries' average smoking prevalence. Therefore, authors propose that efforts in tackling general smoking have to be intensified as this strategy might indirectly decrease smoking among adolescents, in particular among girls.[82]

There is some evidence indicating that the impact of various anti-smoking policies often differs for adults and youth. Bans on tobacco advertisements have yielded mixed results in relation to their effects on adult smoking,[39] but among adolescents evidence indicated that pro-smoking advertisements were more easily recalled[42] and that exposure to cigarette promotions was associated with higher likelihood of adolescents initiating or continuing tobacco use.[43] In contrast, public smoking restrictions and bans appear to be more effective for adults rather than adolescents.[41, 83] There is however some evidence indicating that in some instances restrictions and bans on sales to children and adolescents has reduced smoking and cigarette consumption in this age group.[44]

In addition, the role that mass media can potentially have in both preventing the initiation of tobacco use and supporting cessation in adolescence is sometimes underestimated; for example, tobacco-industry counter-advertising can contribute in "creating" smoke-free environments in films, TV series, music videos etc. and in so doing reduce the presence of direct and indirect messages promoting smoking as "cool" and socially acceptable.[18] There have been mixed results regarding the efficacy of anti-smoking media campaigns on adolescent tobacco use, with some studies reporting little or no effect on younger people in comparison with other groups,[84, 85] and others[86] reporting that media based state-sponsored anti-smoking campaigns were associated with smoking reduction among youth. In addition, health warnings on cigarette packets were found to have little impact in reducing smoking; nevertheless, warnings on plain white packages appeared to be more effective than warnings on traditional cigarette packages.[87]

There is a policy-based movement afoot which seeks to phase out tobacco by restricting access to the individuals born after the year 2000.[88-90] Known as the "tobacco end game" the rationale is that given the known health consequences of tobacco use and the highly addictive nature of the product, tobacco products would fail to be approved by national health authorities if they were submitted for approval now. [88-90] While a complete ban would not be accepted by the general public, a partial ban appears to be acceptable.[89] The "end game" strategy proposes that individuals born in or after the year 2000 have their supply of tobacco products restricted.[89] This strategy has gained support from a variety of groups including the British Medical Association.[88]

RECOMMENDATIONS:

- Increasing the price of cigarettes is a particularly effective for reducing smoking initiation, and quitting or reducing smoking among adolescent tobacco users and should be employed by all governments as a priority (Level of Evidence A).
- Exposure to cigarette advertising is associated with higher likelihood of adolescents initiating or continuing tobacco use. Governments should as such ban tobacco advertising as a priority (Level of Evidence B).
- Governments/health ministries should restrict the sale of tobacco to children and adolescents in order to reduce smoking and cigarette consumption in this age group (Level of Evidence B).

3.3 COUNSELLING

There is good evidence that counselling is the most effective cessation intervention for adolescent tobacco users.[13, 15 16] Counselling strategies have been shown to reduce daily cigarette consumption short-term abstinence among adolescents and, and there is some evidence to indicate intervention may increase the likelihood of long term smoking abstinence.[11, 13, 15]

Types of Counselling

A variety of counselling based intervention formats have been tested in adolescent populations including: brief interventions, motivational enhancement, motivational interviewing, cognitive behavioural therapy, stage based interventions and contingency management. Often more than one approach is used within the counselling interventions.

Brief Interventions

Brief interventions are short, problem-specific approaches for the treatment of health risk behaviours. As their name suggests, brief interventions generally take very little time, with their duration lasting as little as 30 seconds, or extending over a few sessions lasting 5-60 minutes.[91-93] These brief contacts involve making the most of the opportunity to raise awareness, share knowledge and advise persons to consider making changes that improve their health and behaviours. In the smoking cessation field, brief interventions may act as a first step in the treatment process and determine if the smoker can stop or reduce on their own, as well as serve as a method to change specific behaviours before or during treatment. Clinicians and other health care professionals can use brief interventions both as stand-alone interventions, and as an addition to other forms of tobacco use treatment.[94]

Motivational Enhancement

Motivational enhancement approaches, and mainly motivational interviewing (MI), is a popular approach in adolescent smoking cessation interventions.[95] MI is a person-centered method to enhance an individual's motivation and confidence to change harmful behaviours by the development of a discrepancy between current behaviour and future goals, support of autonomy, expression of empathy, and resolution of ambivalence to support behaviour change.[95] A review by MacGowan & Engle (2010) reports that MI has met the American Psychological Association's criteria for promising interventions in adolescent substance use. MI differs from other treatments in that its purpose is not to impart information or skills. Rather, MI emphasizes exploring and reinforcing a clients' intrinsic motivation toward healthy behaviours while supporting their autonomy.[97] Motivation Enhancement Therapy (MET) is an adaptation of MI. MET counselling strategies are personalized and objective feedback is incorporated and delivered using the MI framework.

Cognitive behavioural therapy (CBT)

Cognitive behavioural therapy (CBT) and social cognitive theory (SCT) are based on the assumption that smoking behaviour is initiated and further maintained due to dysfunctional thoughts and emotions; therapy is built upon teaching withdrawal symptom management techniques and developing self-regulation and self-management in order to prevent relapses. Moreover focus is given to stress management, positive reinforcement and techniques that increase self-efficacy.[18] SCT, a variant of CBT, proposes that smoking behaviour may be altered by modifying social interactions among different cognitive, environmental and behavioural factors in order to promote smoking abstinence.[14, 98]

Stage-based Interventions

The transtheoretical model of change (TTM) proposes that abstinence is achieved through a series of stages of change: Pre-contemplation (not yet acknowledging that there is a problem behaviour that needs to be changed), Contemplation (acknowledging that there is a problem but not yet ready or sure about wanting to make a change), Preparation (getting ready to change smoking behaviour in the very near future), Action (actively changing smoking behaviour) and Maintenance (maintaining the behaviour change for more than 6-months).[99,100] TTM-based interventions seek to match intervention tactics to an individuals stage of change, in order to move an indivdiual to action.

Incentive-based interventions

Incentive-based interventions also known as Contingency Management (CM) is a behavioural treatment in which desired behaviours, such as smoking abstinence, are directly reinforced with rewards (e.g., vouchers, cash).[101] Among adult substance users, contingency management has demonstrated efficacy reducing use of

many substances, including tobacco.[102, 103] Based on operant conditioning these interventions follow two simple principles: first, that substance use is maintained by the reinforcing effects of the drug, and second, that substance use can be decreased by the availability of alternative, non-drug reinforcers. Implementation of these interventions can however be challenging due to the need for rapid, accurate monitoring of tobacco use and immediate delivery of rewards for abstinence.[104]

Evidence to Support Type of Counselling

The counseling interventions with the strongest level of evidence to support them are those which employed motivational enhancement, stage-matched interventions, and cognitive behavioural therapy (CBT).[13, 15] Specifically, there is evidence to suggest that interventions that include attitude change, goal setting, self-monitoring, development of coping and problem solving skills, and self-efficacy, as well as interventions that aim based on motivation enhancement and resistance to social pressure, have been associated with better smoking cessation outcomes both in adults and adolescent smokers.[12, 13, 31, 105]

In sections 4-7 we examine the use of counseling based strategies in various settings and delivery channels including health care settings, schools, community and via information technology.

RECOMMENDATIONS

- There is good evidence that counselling is the most effective cessation intervention for adolescent tobacco users (Level of Evidence A).
- The counseling interventions with the strongest level of evidence to support them are motivational enhancement and cognitive behavioural therapy (CBT) (Level of Evidence B).

3.4 PHARMACOTHERAPY

First line pharmacotherapies have been approved for use in adult populations who aim to quit smoking based on strong evidence regarding their efficacy in increasing rates of long-term abstinence. These include nicotine replacement therapies (NRTs) and non-nicotine medications, which provide low-doses of nicotine to assist with managing withdrawal and cravings. A variety of NRT delivery products are available in Europe including: transdermal patches, chewing gums, nicotine lozenges, sublingual tablets, inhaler, nasal and mouth sprays. Non-nicotine pharmacological treatments include bupropion hydrochloride and varenicline; both have been shown to reduce cravings and other withdrawal symptoms.[106, 107]

3.4.1 Nicotine replacement therapies (NRTs)

Seven trials have been conducted in health care settings assessing the effectiveness of NRTs in adolescent smokers, most of them focusing on the nicotine patch. Specifically, the effect of the nicotine patch on long-term abstinence in adolescent smokers has been examined in four randomized double-blind placebo controlled[20, 21, 24-26] and three open-label trials, one of which used a randomized design.[22, 108, 109] Five of these trials were conducted in the US, and, in all but one study[25, 26] the nicotine patch was provided in combination with individual or group-based behavioural interventions. A trend toward significance was reported in only one study.[24]

Trials in adult smokers have shown that the use of NRTs support the reduction in craving, withdrawal symptoms and the number of cigarettes smoked, a necessary condition for achieving smoking cessation.[110, 111] Adolescents too experience craving and withdrawal symptoms.[23, 112] However, evidence suggests that nicotine patch does not alleviate all withdrawal symptoms in adolescent smokers in the long-term, and may therefore be of limited efficacy. More specifically, at least two studies[23, 24] have found that adolescent users of active nicotine patch do not differ for withdrawal symptoms from the placebo patch users. Another two studies found that the use of the nicotine patch was associated with less craving and lower withdrawal symptom scores,[20, 22] especially among those who were abstinent,[20] however, neither study showed any effect on continuous abstinence.

Several studies have also assessed the effect of the nicotine patch on the reduction of the number of cigarettes smoked per day. Some trials have shown reductions in cigarettes smoked at end-of-treatment.[22, 109] However, those that used controls have shown that the observed reductions were not associated with the treatment group[24, 108] suggesting that the use of the nicotine patch was not more effective. More recently, an open-label study assessed the effectiveness of the combined use of cognitive behavioural motivational enhancement therapy and nicotine patch in a sample of 34 adolescents (mean age 19 years, SD: 1.9) and found that young smokers reduced the number of cigarettes smoked per day and severity of nicotine dependence significantly.[113] However the open-label design of the study and the optional nature of the use of nicotine patch obscure the possible benefits of nicotine patch therapy.

Sparse evidence is available regarding the efficacy of nicotine chewing gum and nasal spray in the adolescent population. In the case of nicotine gum, evidence comes from one randomized double-blind placebo-controlled trial[24] and one randomized open-label trial.[108] One open-label RCT has tested the use of nasal spray in the adolescent population.[114] None of these trials showed a long-term benefit of these aids for adolescent tobacco users.

Adverse health effects from the use of nicotine patches are minor and include local skin reactions,[24-26,109] headache,[20-22] nausea/vomiting,[21, 23] tiredness, sleep disturbances, joint/muscle ache,[24-26] and light headedness/dizziness.[21, 115]

RECOMMENDATIONS:

- Nicotine Replacement Therapy (NRT) is recommended as a second-line therapy for daily adolescent tobacco users who are dependent on nicotine (Level of Evidence B).
- It is recommended that NRT be used in combination with counselling to maximize cessation outcomes (Level of Evidence A).

3.4.2 Bupropion

Bupropion is a non-nicotine therapy for smoking cessation available in tablet form by prescription only which has been shown to be effective in increasing rates of smoking abstinence in the general population of tobacco users.[28, 116]

Five RCTs,[117-121] and one open-label study[122] have been conducted in health care settings focusing on the efficacy of bupropion hydrochloride (sustained release SR or XL) on smoking cessation among adolescent smokers. All trials but one[121] were conducted in the USA. All trials but one[118] included some kind of a behavioural counselling component in addition to medication. One trial included bupropion in addition to the nicotine patch.[119]

Among the trials with relatively large samples, one trial[120] reported that high dosages of bupropion might be more efficacious for smoking cessation than placebo during the treatment phase, but not following treatment (i.e., significant differences in quit rates between the groups disappear after the discontinuation of the medication). In contrast to studies conducted in adult smokers,[123] bupropion SR seems to have no effect also when it is used as an adjunct to nicotine patches in adolescents.[119] One RCT found bupropion SR's use may yield promising results when combined with contingency management.[117]

There is weak mixed evidence to support the use of bupropion SR for achieving intermediate treatment goals, such as the reduction of the number of cigarettes smoked per day and the reduction of withdrawal symptoms. One large trial comparing the efficacy of the combined use of bupropion and nicotine patch versus nicotine patch and placebo bupropion found that the combined intervention did not result in a statistically significant difference in the reduction of craving scores over time.[119] A study by Niederhofer and Huber found no differences in the reduction in the number of cigarettes smoked per day between adolescents in bupropion group and those receiving placebo.[121] However, evidence from at least one study found that bupropion was effective in reducing the number of cigarettes smoked per day, as well as reductions in exposure (carbon monoxide levels), withdrawal symptoms and cravings in adolescents smokers.[122]

Data on the adverse health effects associated with the use of bupropion are available from at least four trials involving a pooled total of 407 adolescent smokers.[13, 117, 119-121] Adverse events were mild and included: headaches, insomnia, irritability, and dream disturbances.[13, 117] No increased risk explicitly associated with the use of bupropion was reported by Killen and associates (2004) and Niederhofer and Huber (2004).[121] Approximately,

4% of the participants in the study of Muramoto and colleagues (2007)[120] reported adverse effects. In two cases participants were hospitalised for drug and other substance use-related events. Finally, adverse effects from the use of bupropion were reported by a significantly greater proportion of bupropion users compared to the placebo group only in the trial conducted by Gray and colleagues (2011).[117]

In summary, evidence regarding the effectiveness of the use of bupropion on smoking cessation in adolescent smokers is based on a limited number of trials and suggests that the drug does not have a persistent effect on smoking abstinence.[13, 14, 124]

RECOMMENDATIONS:

- There is insufficient evidence to support that bupropion can be an effective cessation aid for adolescent smokers who are dependent on nicotine (Level of Evidence C).

3.4.3 Varenicline

Varenicline is a partial agonist of the α4β2 nicotinic acetylcholine receptor, offering a two-pronged approach to treating the addiction: as a partial agonist of the nicotinic receptor, this drug reduces the symptoms of nicotine withdrawal, while it simultaneously blocks some of its reinforcing effects. Varenicline produces approximately fifty percent (50%) of the receptor stimulation provided by nicotine, and blocks the effects of nicotine inhaled from cigarette use.[142] There is strong randomized controlled trial evidence that varenicline increases rates of smoking abstinence among adult tobacco users and has found to be superior to both NRT and bupropion.[28, 116] Varenicline is however. not currently approved among adolescents.

Three trials have examined the use of varenicline on smoking in adolescent tobacco users.[117, 126, 127] One of these was small and compared varenicline with bupropion, but included no placebo control.[117] This trial found no-effect of varenicline on smoking abstinence. Faessel and colleagues (2009)[126] conducted a multicenter, randomized, double placebo-controlled, parallel-group trial in order to examine the pharmacokinetics, safety, and tolerability of varenicline in adolescent regular smokers aged 12 through 16 years. Participants were first classified in two groups according to their weight—high body weight (>55 kg; n=35) and low body weight (≤55 kg; n=37). Adolescents were then randomized to receive a dose equivalent to a standard adult dose (1.0 mg twice daily for those weighting >55 kg, and 0.5 mg twice daily for those weighting ≤ 55 kg), a lower dose (0.5 mg once daily) or placebo for 14 days. The study showed that higher varenicline dosage was associated with greater reductions in smoking at 16-day follow-up only among participants with high-body weight. Among participants with low body weight, reductions in smoking were similar across standard dose, low dose and placebo conditions. Another trial testing varenicline's efficacy among adolescents was underway when the present review was conducted.[127, 128]

No serious adverse events associated with the use of varenicline were reported in the study by Gray and associates (2012).[118] Faessel and colleagues (2009)[126] found that the only treatment-related psychiatric adverse events were abnormal dreams (n=2) and transient anger (n=1), but these effects were considered to be mild.

In summary, owing to the limited number of studies conducted, there is still insufficient evidence about the effectiveness of the use of varenicline on smoking cessation in adolescent smokers. More research is needed to assess the value of varenicline in adolescent smoking cessation.

RECOMMENDATIONS:

- There is insufficient evidence to support the use of varenicline as an effective smoking cessation aid for adolescent smokers who are dependent on nicotine (Level of Evidence C).

3.5 Other Interventions

3.5.1 Acupuncture

Acupuncture is a traditional Chinese therapy; it is generally performed using fine needles inserted through the skin at specific points of the body. Needles can be stimulated by hand or by using an electric current (electro-acupuncture). Other related therapies, in which points are stimulated without employing needles include acupressure, laser therapy and electrical stimulation.[129] Currently, there are two approaches to explain the effect of acupuncture. In the traditional approach (Traditional Chinese Acupuncture, TCA), the needles are inserted into particular locations where, it is believed, they can correct disturbances of a force called qi that underlie the patients' illness. Other locations are not believed to have this special property, and therefore can be readily used as placebo control. This is the theory that underlies most trials of acupuncture. In a more recent approach, known as Western Medical Acupuncture (WMA,) the effect is thought to be the result of stimulating nerves or connective tissue.[130]

Two trials conducted in health care settings have tested the effectiveness of acupuncture on smoking cessation among adolescent tobacco users. In a case control study, Kang et al. (2005) tested acupuncture in a sample of Korean adolescents attending high school. A double-blind RCT by Cai et al. (2000) was conducted in a sample of Singaporean adolescent tobacco users attending a smoking cessation clinic where acupuncture was offered as an alternative to the standard counselling. In Kang et al (2005)[131] study the intervention group received metal acupuncture with the use of adhesive paper, whereas in that study of Cai and colleagues (2000)[132] received laser acupuncture. In both studies the control group received some kind of "placebo" acupuncture. In the Kang et al (2005)[131] study rates of smoking abstinence were very low in both the intervention group (0.6%) and control group (0%) after 4 weeks. Moreover, differences between intervention and control groups on secondary out-

comes (change in the taste of tobacco, intensity of the desire to smoke, reduction in cigarette consumption) were not significant. Cai and colleagues found no significant differences between intervention and control groups at end of the 4-week treatment period nor the three-month follow-up (OR= 0.971, CI=0.53-1.77). Both groups documented an increase in smoking abstinence at the 3-month follow-up (24.8% and 26.2% for intervention and control respectively) and the majority (80%) of participants reported a reduction in daily tobacco use.

In summary, our review has found no evidence to support that acupuncture treatment is effective in adolescents' smoking cessation.

RECOMMENDATIONS:

- Acupuncture is not a recommended treatment for smoking cessation among adolescents within health care/medical settings (Level of Evidence C).

4.0
HEALTH CARE / CLINICAL SETTINGS

Health care settings, both primary care and secondary care, offer important opportunities for delivering cessation interventions that target adolescent smokers. Health care services can reach a wide diversity of adolescents, including those who are less connected to their school and less interested in quitting smoking.[133, 134]

In Europe, two-thirds of children and adolescents aged 8–18 years will visit a health care professional at least once a year, with the mean number of visits being 2.5.[27] In the UK, around half of 14-15-year-old students had visited their doctor in the past three months; and 4-10% will be admitted to hospital.[75] Both office visits and hospitalization offer important opportunities for address tobacco use and cessation with adolescents. In the case of hospitals this includes both general admissions and admissions to mental health facilities. Compared to their non-smoking peers, adolescent smokers are also more likely to have seen a doctor or other health professional for emotional or psychological complaints.[47] For example, an estimated 72% of 16-year-old "ever" tobacco users in Greece visited a doctor for a health related problem in the past year, a higher proportion compared to never-smokers (67%).[135] Dental care professionals, in particular, are in the unique position to identify and intervene with tobacco users. More than half (57%) of individuals aged 15 to 24 years in the European region have visited their dentist in the past year, with the average number of visits being 2.4 per year.[136] Dental care requires frequent contact over an extended period of time, providing a mechanism for long-term assessment and reinforcement. In addition, dentists are able to communicate tobacco cessation advice in the context of the effects of tobacco use on oral health.[137, 138] Data from the US[139, 140] and Finland[141] suggests that adolescents would be willing to speak to health care professionals regarding their intention to quit and receive recommendations on treatments.[142, 143]

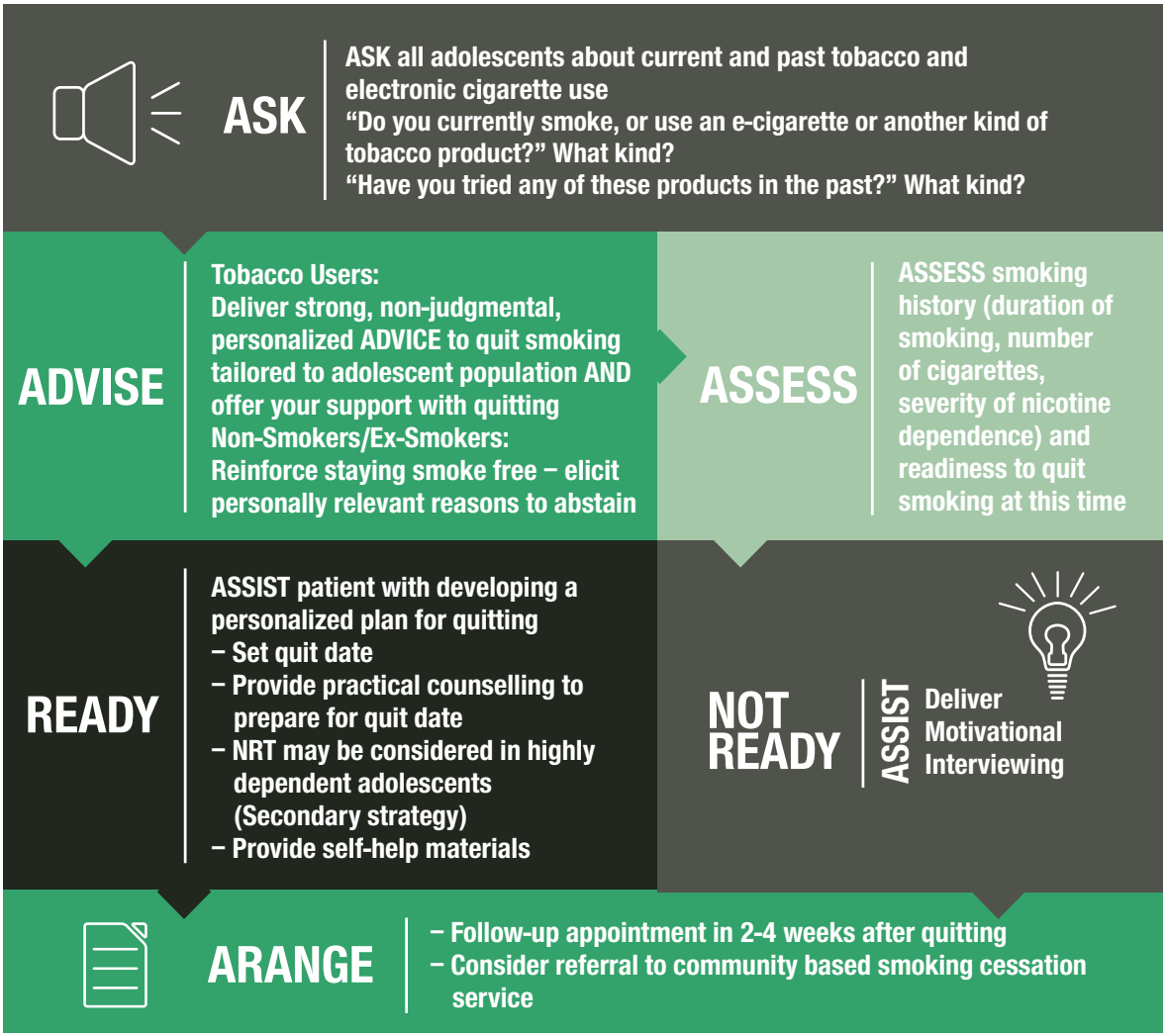
Health care professionals have a very important role in terms of preventing tobacco use and supporting cessation among adolescents. Office-based brief clinician interventions have been found to promote smoking cessation in adult tobacco users,[28, 141, 143-149] this has led to expert consensus of the importance of early identification of smoking status and the delivery of brief interventions to promote tobacco cessation in adolescents as well.[28] Specifically, clinicians are urged to incorporate brief, "5A's" (Ask, Advise, Assess, Assist, Arrange) interventions into their routine clinical practice. **Figure 1** provides an overview of the "5As" model.[28, 92, 143, 144] The model in-

volves "asking" about tobacco use, delivering brief non-judgemental "advice" to quit, "assessing" readiness to quit and smoking history, "assisting" with cessation using evidence-based techniques, and "arranging" follow-up. Due to the increased use of electronic cigarettes as well as other forms of tobacco among adolescents, health care professional should ask about both tobacco and electronic cigarette use and use of alternative forms of tobacco such as chewing gum, cigars, hookah.

RECOMMENDATIONS:

- Health care providers should ask all adolescent patients about both tobacco use and electronic cigarette use (Strength of Evidence A).
- Current tobacco users should be counselled about quitting smoking and referred to evidence-based resources to support cessation when indicated (Strength of Evidence B).
- Health care professionals should tailor advice to quit smoking to adolescent tobacco users by focussing on the short and long-term health effects, personal hygiene (smell, bad breath), implications for athletic performance, attractiveness, and the cost of tobacco use in the short and long-term (Strength of Evidence C).
- Health care providers should receive smoking cessation training to increase skill in addressing adolescent tobacco users among adolescent tobacco users (Strength of Evidence A).

FIGURE 1: TOBACCO TREATMENT PROTOCOL FOR ADOLESCENTS



4.1 Behavioural interventions in health care settings

We review here counselling based (behavioural) interventions that have been tested in health care settings.

4.1.1 Brief Interventions

Between 2000-2016, four RCTs have tested brief interventions in adolescent populations in clinical settings.[138, 141, 146, 148] All four of these studies were conducted in dental health environments; among them three were conducted in Finland and one in the US.[147] The three Finish studies[138, 141, 148] assessed the long-term effects of a simple brief intervention compared to standard care and produced relatively high (over 15%) abstinence rates in the treatment condition, but no statistically significant differences between conditions. The US trial employed an enhanced brief intervention and yielded negative effects at follow-up.[146] All four trials had relatively weak designs, which may have contributed to the lack of significant outcomes.

Specifically, one Finish study randomized 127 adolescent smokers (15-16-years of age, 52% girls) into a dentist-led intervention (n=37/44), a school-nurse led intervention (n=29/41), or a control group (n=28/39).[141] The two intervention groups received a 24- and 49-minutes of contact time, respectively based on the "5A's" model. The control condition included a leaflet about the harmful effects of smoking. At the 3-month follow-up self-reports indicated that 22% of the participants in the dentist's group reported abstaining from smoking, compared to 21% in the nurse's group, and 11% in the control group. However, the small number of participants coupled with the lack of the bio-chemical validation of abstinence reduces substantially the strength of this evidence.

A controlled trial originally conducted in Finland in 1992,[138] randomized 2,586 12-year-olds to either a brief intervention (n=1348), which exposed participants to photographs of teeth discoloration or a standard dental care group (n=1238). Difference between the conditions in terms of effects on smoking abstinence was non-significant (RR=1.09, 95% CI: 0.87-1.36). Almost 16 years later, in 2008, the same group followed that cohort with the aim to assess the possible long-term effectiveness of the brief intervention.[148] They managed to complete follow-up with 529 (39%) and 491 (35%) of the participants from the original intervention and control group, respectively. Approximately 15% of participants in the intervention group and 19% of those in the control group reported current smoking at the age of 30 years, a non-significant difference.

Despite the limited evidence regarding the efficacy of brief interventions to support cessation among adolescents, based on evidence generated from adult populations brief interventions are recommended strategies for intervening with tobacco users in clinical settings.[28]

4.1.2 Motivational enhancement & motivational interviewing

From 2000 onwards, six trials were published which tested the efficacy of MI interventions delivered in health care settings on smoking cessation among adolescent smokers. All trials used samples of adolescent smokers from the US. All but one study[150] used a randomized controlled study (RCT) design and instead used a control group in which brief advice was given. Two out of the six trials implemented a cessation intervention in special populations; these included adolescent smokers with psychiatric disorders,151 and outpatients in a substance abuse program.[150] Two of the studies[133, 150] involved solely face-to-face motivational interviewing, while, the rest, included also some other component. Brown and colleagues (2003)[151] additionally used a relapse prevention manual and a self-help pamphlet, Colby and colleagues (2012)[152] included a follow-up call of 15 to 20 minutes one week after the initial session and a brief telephone-based parent intervention. Horn and colleagues (2007)[153] included a homework book, a handwritten postcard within 3 days of the intervention and motivational phone calls. None of the trials reported significant results on smoking cessation. However, some of these trials yielded significant results on outcomes that can potentially mediate cessation, mainly regarding the reduction of cigarettes smoked per day in the intervention groups.[133, 150, 153]

Interventions tested to date vary largely regarding treatment format or modality (e.g., group, individual, telephone, in-person, use of technology), and design (e.g. providing assessment and feedback, pre-treatment adjunct, or post-treatment follow-up). Understanding the influence of these characteristics may assist with understanding the sub-population of smokers who benefit most from MI interventions and improving the design of future interventions targeting adolescent tobacco users.

Apart from intervention characteristics, understanding the possible underlying mechanisms of change in MI interventions can also improve effectiveness.[98] Based on evidence from addiction centers[102] MI's effectiveness is associated with client's language preference, experience of discrepancy, and certain techniques, such as decisional balance. However, they also reported that evidence for client readiness, client engagement, client resistance, and client confidence was inconsistent. They concluded that although the theories underlying MI are rich, they are not integrated into a formal and comprehensive theory, making it difficult to pursue investigations on the mechanisms of change. Applying more theory-based structure to MI intervention design and content appears warranted.[97]

In summary, although none of the interventions resulted in significant increases in rates of smoking cessation (i.e., effect sizes tend to be small), some of them showed some promise in reducing the number of cigarettes smoked per day. There is as mixed evidence regarding the efficacy of MI in achieving cessation in adolescent populations, however good evidence that MI produces reductions in smoking consumption in the adolescent populations.[133, 150, 153] Most studies of MI interventions in adolescent are small, which limits their quality. Further research; to better understand the role of MI in adolescent populations, in needed.

4.1.3 Transtheoretical Model of Change (TTM)

A small number of TTM interventions have been evaluated for adolescent smoking cessation in health care settings. Specifically, from 2000 onwards, three RCTs were published which tested efficacy of TTM-based interventions on smoking cessation among adolescent smokers (n=808 randomized adolescent smokers). Two of these trials used samples of adolescent smokers from the USA[154, 155] and one from Finland.[76] Of the three trials, only one by Hollis and colleagues' (2005)[154] yielded a significant effect on smoking cessation outcomes. Abstinence rates after 2 years were significantly higher for the intervention group, relative to the control group (OR=2.42; 95% CI: 1.40-4.16) for current smokers however no effect was observed for adolescent who had "experimented" with tobacco use in the past month.[154] Study findings suggest that it is advisable for intervention protocols to separate smokers from "experimenters" and tailor interventions to these sub-groups.

4.1.4 Incentive-based Interventions

From 2000 onwards, only one trial was published which tested the efficacy of incentive-based interventions delivered in health care settings on smoking cessation among adolescent smokers. Findings suggest that combined treatment may be superior to CM alone, at least during treatment. While this trial has yielded some promising results, additional research is required to better understand the value of incentive-base interventions in supporting cessation in adolescent smokers.[117]

RECOMMENDATIONS

- Health care professional should be prepared to deliver brief counselling based interventions to adolescent patients who smoke that is tailored to their stage of change (Level of Evidence B).
- Counselling interventions based on motivational Interviewing are effective in reducing daily tobacco use among adolescents and are as such recommended interventions (Level of Evidence B).
- There is insufficient evidence to recommended incentive-based intervention as a smoking cessation aid for adolescent smokers in health care settings (Level of Evidence C).

5.0
SCHOOL SETTINGS

Schools, and educational settings, have the potential of offering effective smoking-cessation interventions and there is evidence to suggest that these settings are preferred by adolescent tobacco users compared to health care or other settings.[30] A meta-analysis of 48 trials involving adolescent tobacco user concluded that tobacco cessation programs are more likely to be effective if they are offered within the school setting (classroom and school clinic).[31]

School-based interventions have several advantages including high rates of access to adolescent populations. In most developed countries more than 90% adolescents attend school or are associated with some form of formal education.[156] Likewise, school health practitioners are easily accessed by students, without parental involvement, and can provide on-going support with no cost.[157] Where available, school health practitioners (most commonly, nurses) may be equipped with the appropriate skills and credibility to offer specialised assistance that can support smoking cessation. The school setting is also ideal for conducting long-term interventions (interventions that extend over the entire annual academic period). School environments also allow for enhanced communication and engagement with peers, teachers, and parents as all these groups can be part of comprehensive, multi-level interventions to prevention and smoking cessation.[158] In addition, given the increasing role of internet and novel ICT applications, schools can offer access to computers and online services to all students, thereby making possible the implementation of interventions that include technology as the key intervention medium.[159] Finally, schools are the appropriate settings also to target youth of higher risk of smoking-related adverse effects, notably youth with poor academic performance, repeated suspensions, conduct problems, drug use etc.[160, 161]

This section reviews the available evidence pertaining to the effectiveness of interventions implemented in the school setting. Accounting for differences both between and within countries, the review included both classroom-based and school-clinic interventions. Classroom-based interventions refer to interventions delivered within intact classrooms as part of a classroom course.[12, 35] School-clinic interventions refer to the implementation of private structured interactive sessions for small groups of students who voluntarily or compulsory seek tobacco cessation assistance. The latter are delivered in a designated classroom or office but outside of the

regular classroom context. Generally, 'clinics' operate during school hours and participants are released from class to attend the clinic.[12, 30, 162]

The vast majority of tobacco cessation interventions implemented in the school-setting use psychosocial approaches to cessation, including fact-based, attitudinal educational approaches; only a small number of school-based interventions have combine psychosocial approaches with pharmacotherapy.[13]

5.1 Behavioural interventions in school settings

5.1.1 Brief interventions

At least two trials have evaluated the effects of school-based 'enhanced' brief interventions in smoking cessation, and both have documented short-term effects on smoking cessation.

Specifically:

A US-based RCT evaluated the effectiveness of a school nurse-delivered smoking-cessation counselling intervention for adolescent smokers based on the 'Calling It Quits" counselling intervention protocol — a CBT enhanced version of the "5 A's" model adapted for adolescents.[140] Adolescent smokers were randomized to either the intervention (n=486) or a control condition (n=582). Compared to the control group, the intervention group documented a reduction in the number of cigarettes smoked, number of days smoked (in the past 7 days), and significantly higher saliva cotinine-validated cessation rates at the 3-month follow-up (OR=1.90, 95% CI: 1.12–3.24), but only among male students (10% vs. 2%); effects were not sustained at the 12-month follow-up.

In Denmark, Dalum and colleagues (2012)[147, 163] conducted a RCT of a smoking cessation intervention designed for daily smokers attending 22 alternative schools (mean age 17.7 years; n=514 at 1-month and n=369 at 14-month follow up). The intervention involved a short 3- 5-minute motivational interviewing counselling session and a range of self-help materials. The study found positive short-term effects regarding smoking cessation (5% vs. 2% in control; adjusted OR=4.50, 95% CI: 1.20–16.86), but the effect did not maintain at 12-month follow up (8% vs. 7%).

Taken together, although limited, the available evidence indicates that school-based brief smoking-cessation interventions which are enhanced by cognitive behavioural and are delivered by school nurses can be effective in promoting at least short-term abstinence among adolescent smokers.

5.1.2 Motivational enhancement / interviewing

Many school-based programs have relied on motivation enhancement to achieve abstinence.[13] Among them, Project EX stands out as an important evidence-based smoking cessation program for adolescent smokers.[33, 34] Project EX is based on the premise that a lack of motivation is an important independent factor for unsuccessful smoking cessation in adolescents; other factors may include social influence and nicotine dependency. Originated and implemented mainly in the US, Project EX consists of 8 40-45 minute group-based sessions delivered over a 6-week period, and uses a motivational enhancement framework in conjunction with additional components (e.g., games, yoga and meditation) to increase coping strategies when trying to quit smoking or maintain quit status, and to increase awareness of the reasons for participants to discontinue smoking.[33] The first two weeks of the program focus on preparing for quitting. Participants are asked to make a quit attempt at the end of the second week of the program. The final four weeks of the program focus on strategies for maintaining smoking abstinence. Trained counsellors deliver the group-based sessions during school hours.

Table 3: Overview of the Project EX Curriculum

SESSION NAME	CONTENTS
Orientation	– Imparts the ground rules for the class and discusses reasons for using, not using, quitting tobacco, or remaining tobacco free
Tobacco affects your life	– Discusses how tobacco use can cause, rather than relieve stress
Health dangers of tobacco use	– Discusses the harmfull substances in tobacco and how it can injure one's body
Quitting step 1-Making a commitment about not using tobacco	– Discusses addiction to tobacco. Methods of quitting and physical and psychological aspects of withdrawal are discussed
Quitting step 2 -Managing withdrawal symptoms	– Discusses more about nicotine, addiction and strategies of avoiding addiction or managing withdrawal symptoms. Psychological coping includes self-forgiveness and avoiding false expectations regarding how not using tobacco or quitting will and will not affect one's life

SESSION NAME	CONTENTS
Taking care of a healthy body	– Involves learning lifestyle balance strategies, including weight control and practising a "yoga activity"
Taking care of your piece of mind	– Involves learning more coping strategies, including assertiveness training and anger managment. Participants also learn the "letting feelings pass" meditation activity
Not smoking again: commitment and avoiding relapse	– Involves learning means to avoid using tobacco again, or staying tobacco free, and mentions how topics covered in the tobacco education program could be applicable to other substances

Source: Gonzálvez et al 2015[164]

Evidence from five trials (with different strengths and weaknesses) indicates that Project EX is effective in producing promising short-[35, 165] and long-term[33, 59, 166] effects on prolonged (30-day) smoking cessation and a reduction in cigarette consumption.[165, 166] Importantly, the implementation of Project EX has been associated with significant increases in the levels of motivation to quit smoking both during and following treatment[59] as well as decreases in future smoking intentions and nicotine dependency scores.165 Project EX has also been implemented outside the US.[167]

PROJECT EX
The official site of Project EX is www.projectex.usc.edu
A brief, technical presentation of Project EX can be found at: www.theathenaforum.org/sites/default/files/Project%20EX%204-21-12.pdf).
For an overview of Project EX see Sussman et al 2014[161]

In addition to Project EX, at least seven school-based trials have assessed the effectiveness of motivational enhancement interventions.[153, 168-172] Three[168, 171, 172] were US-based and met the criteria for inclusion in Stanton and Grimshaw's 2013 Cochrane review.[13] Two studies were conducted in South Korea[169, 170] with their results published in Korean. All trials showed positive short-term outcomes, but none showed significant effects on abstinence at 6-months or longer. Specifically, there is only one relatively large study that examined long-term effects on smoking abstinence.[172] This study used telephone-delivered motivational interviewing that included school-based print and electronic media and access to a stage-tailored website (n=25 schools; n=1,058) as compared to no-intervention (n=25 schools; n=1,093).[172] The study found that participants in the treatment group had higher self-reported 7-day (48% vs. 40%), 1-month (36% vs. 29%), and 6-month (22% vs. 18%) prolonged abstinence rates, compared to the control group, but the effect at 6 months was non-significant (RR=1.60; 95% CI: 0.94-2.71).[13]

Other rather small studies have assessed secondary cessation outcomes. Kelly and Lapworth (2006)[171] compared the effectiveness of a 1-hour motivational interview session to standard care (advice/education) in 15-year-olds referred by school administrators because of tobacco use (n=56). The study showed significant short-term reductions in the quantity and frequency of smoking relative to standard care, but positive effects were not maintained at the 3- or 6-month follow-up. Colby and colleagues (2012)[152] compared an enhanced motivational interviewing condition (n=79) to a brief advice session (n=83) among 16-year-olds who smoked at least once a week. In addition to an individual session of motivational interviewing the intervention arm comprised a 1-week telephone booster session and a brief parenting intervention (all with a 15–20-minute duration). The participants in the motivational interviewing condition significantly reduced the number of cigarettes they smoked at 1-month follow-up, but no differences were observed between conditions at 6-month follow-up (5% vs. 3%). Finally, two separate studies in South Korea assessed the effectiveness of a motivational interviewing-based smoking cessation program using non-equivalent control group pre-test-post-test design (i.e. school classes had similar characteristics but students were not allocated at random to conditions).[169, 170] Authors reported a significant decrease in cigarettes smoked per day and urinary cotinine levels in the experimental group, compared to the control group.

Taken together, evidence pertaining to the effectiveness of in school-based programs suggests that motivational enhancement can yield positive short-term primary (abstinence) and secondary cessation effects such as decreased cigarette consumption, frequency of smoking, as well as the advancement of future non-smoking expectations. More studies, with larger samples, are warranted to confirm possible long-term (3-months or longer) effects on cessation.

5.1.3 Cognitive behavioural therapy (CBT) / social cognitive therapy (SCT)

The US-based "Not-On-Tobacco" (NoT) program is a widely used smoking reduction / cessation intervention designed for school-aged youth above 13 years and is grounded in SCT.173 Designed separately for male and female smokers, NoT consists of ten 50-minute group sessions run by trained facilitators (teachers, counsellors, nurses and health educators) during school hours. NoT covers the entire quitting process, including preparing to quit and preventing relapses. It aims specifically at improving life skills especially by making smokers learn to identify their reasons for smoking (cognitive), adopt healthy alternatives to smoking (behavioural), and identify people who will support them in their efforts to quit (environmental).

A number of school-based trials have assessed the effectiveness of NoT,[174-179] all concluding that the program is relatively effective in achieving – if not sustained cessation – a significant reduction in smoking. Specifically, evaluation studies conducted by key NoT investigators have suggested that the program helped approximately 90% (of over 12,000 participants in total) to either quit or reduce smoking, while produced intent-to-treat absolute quit rates between 15% and 19%.[177, 180] Moreover, as one study has shown, the intensive, multi-session intervention has been effective with adolescent smokers with various degrees of nicotine dependency, including high-dependent smokers (as opposed to the brief intervention that produced positive outcomes with only low-dependent smokers).[181] However, using stricter criteria for follow-up assessment (i.e. 6-month follow-up assessment), intention-to-treat analysis conducted in the context of the 2013 Cochrane review[13] suggested that none of the 6 NoT trials published between 2001 and 2011[174-179] individually demonstrated a statistically significant effect–likely attributed to the limited power of the individual trials.[96] In the same review, the pooled analyses of NoT trials produced a statistically significant effect, RR=1.31, 95% CI: 1.01-1.71).

NOT ON TOBACCO (NOT)
For a brief overview of Not on Tobacco (NoT) smoking cessation program see www.cdc.gov/prc/pdf/not-on-tobacco-smoking-cessation.pdf
The official site of NoT: www.lung.org/associations/states/colorado/tobacco/not-on-tobacco/

In addition to the NoT intervention, two recent rather small trials have evaluated the effectiveness of school-based interventions designed using CBT models–each reporting non-significant abstinence effects of the intervention relative to the control condition.

Specifically:

A South Korean study evaluated CBT for smoking cessation among middle school male smokers.[182] Chun et al. (2012)[182] compared a six session CBT intervention (n=35) with a 1-hour education session (n=45) using a pre-test-post-test non-equivalence control group design. Although intervention participants had significantly lower nicotine dependence relative to control condition, there was no significant difference in self-reported or biochemically confirmed abstinence at end-of-treatment.

A cross-national trial[183, 184] assessed the combined effect of CBT and cognitive bias modification (CBM) model – a treatment that aims at retraining automatic impulsive action tendencies – in smoking cessation among adolescent smokers with high impulsivity (n=60; 18 in the US and 42 in the Netherlands). Participants undertook either a 4-week smoking cessation program that combined weekly CBT and CBM delivery to avoid smoking stimuli or sham training. Their treatment outcome was defined as self-reported 7-day-point-prevalence abstinence validated by cotinine levels at end of treatment. Although the results of intention-to-treat analyses found a trend toward higher absolute prevalence of abstinence at end-of-treatment when compared with the sham condition (17.2% vs. 3.2%; p=0.071) the results were non-significant. The abstinence rates at 3-month follow-up did not differ by treatment condition. As significant decrease in the average number of cigarettes smoked and cotinine levels was documented over the course of treatment among all participants regardless of treatment condition.

CBT treatments that specialize on specific aspects of tobacco use may produce promising results. A US-based RCT compared an intervention focusing on stress management and psychosocial aspects of smoking cessation with one focusing on management of "cravings" and withdrawal symptoms.[163] The trial found that those in the groups focusing on stress and psychosocial dependency were almost four times as likely to abstain at the end of treatment. Specifically, the trial randomized 244 regular smokers or smokeless tobacco users from 16 high schools into five 45-minute sessions, which included, either psychosocial dependency treatment (focusing on the social and psychological aspects of tobacco use, including stress management), addiction model treatment (focusing on the physiological aspects of addiction), or a control intervention (a quitting tip sheet). Intention-to-treat analyses indicated 10% abstinence for smokers and 12% for the users of smokeless tobacco at-end-of treatment. At 4-month follow-up, analyses on biochemically verified data indicated 6% abstinence for smoker's at-end-of treatment (versus 3% in the control group, ns) - 14% for smokeless tobacco users (none quitted in the control, $p<0.05$). The study also showed that among smokers who participated in the cessation groups, smokers in the psychosocial dependency groups were more likely to succeed in quitting. Daily use of cigarettes dramatically reduced the likelihood of a participant's quitting: from over 60% cessation to 20% cessation during the intervention.

In summary, school-based programs that are based on SCT yield positive short-term abstinence and decreased cigarette consumption. More studies, with larger samples, are warranted to confirm possible long-term (3-months or longer) effects on cessation.

5.1.4 Stages of change interventions

Four school-based smoking cessation interventions had the transtheoretical model of change (TTM) at their core.[159, 185, 186]

Specifically:

A relatively large and rigorous UK-based trial tested the effectiveness of an interactive self-help intervention which – in addition to a self-help manual – asked adolescents (aged 13-14 years; n=547 in the intervention group) to write down their thoughts and feelings about smoking.[157] Based on their responses automated decision rules created individualised smoking cessation strategies that assisted smokers to move through stages from smoking to cessation and from cessation to refraining from relapsing. A marginal increase in self-reported smoking abstinence was reported at the 12-month follow-up (RR=1.45, 95% CI: 1.01-2.08), although this benefit was not maintained at the 24-month follow up.

More recently, two school-based trials assessed interventions that applied the TTM for achieving behavioural change through text messages. One of these, conducted in China, assessed the effectiveness of a 12-week intervention (n=92) relative to a control condition (information pamphlet; n=87).[186] The intervention provided TTM stage-matched text messages about health risks of smoking, reasonable attitudes towards smoking, strategies to initiate a quit attempt, quitting-related skills, and refusal skills and relapse prevention. In addition to providing stage-tailored feedback via text messages, participants were encouraged to use online chatting to support cessation. The other trial was conducted in Switzerland and tested the efficacy of a 3-month text messaging intervention (n=372) relative to an assessment-only control group (n=383) (mean age=18.2 years).[185] The intervention was informed by a motivation-focused approach to smoking cessation that built upon TTM by identifying the social-cognitive processes (expectancies, risk perception, perceived self-efficacy, planning processes and self-regulation) that contribute to progression from non-active (pre-contemplation, contemplation and preparation) to active stages of change (action and maintenance). Activities included an online smoking assessment, weekly text message-based smoking assessment, two weekly tailored text messages, and a quit day/relapse prevention text message. Although both these interventions yielded higher rates of smoking reduction and – only in the case of the Chinese study – advancement through quitting stages, relative to their respective control conditions, there was no significant intervention effect for 7- or 30-day point prevalence abstinence at end-of-treatment[186] or at 6-month[185] post-baseline.

A relatively small US study assessed a smoking cessation intervention based on a combined TTM and CBT model for adolescent smokers aged 14 through 18 years.[185] Seven schools were randomised into either an intervention group comprising cognitive behavioural therapy tailored to stage of change, a workbook, role play, discussion and games, and a video (n=61), or a control group comprising teaching and information material (n=44). A higher percentage of participants in the intervention group (67%) reported non-daily smoking in the past 12 months, compared to the control group (42%, $p<0.05$). The intervention group also reduced their smoking from an average of 8 cigarettes a day at baseline to 6 cigarettes a day ($p<0.05$). The overall 1-year quit rate for both groups was also higher than the average rate reported elsewhere (12%); however differences were not statistically significant.

Taken together the available evidence suggests that school-based programs may yield positive short-term primary (i.e., abstinence) or secondary cessation outcomes (e.g., advancement through quitting stages and reductions in the quantity and frequency of tobacco use).

5.1.5 Incentive-based interventions in school settings

Psychosocial approaches that rely on incentive-based interventions also known as contingency management (CM) have been applied with some success in adult smokers[187, 188] and have also been considered for promoting abstinence assisting among adolescent smokers.[103]

In school-settings two US trials have assessed the efficacy of interventions that relied on contingency management theory (CM) for achieving behavioural change.[104, 189] Between them, the most recent, and the one with the larger sample size examined the effects of contingency management and CBT, offered separately as well as in combination among 82 adolescent smokers (mean age, 16.1 years).[104] Participants were randomly allocated to the CBT condition participated in weekly, 30-minute therapy sessions. Those in the CM condition were reinforced for abstinence on an escalating magnitude schedule. At end-of-treatment, the 7-day point prevalence abstinence rates for CM alone (n=25) and the combined CM and CBT condition (n=31) did not significantly differ from each other, but produced higher abstinence rates observed for CBT alone (n=26; 36%, 37% and 0%, respectively). There was also some advantage for the combined CM and CBT as regards the day to first cigarette during treatment (CBT alone: Day 3, CM alone: Day 9, combined CM and CBT: Day 20); however, there was no difference observed at the 1- and 3-month follow-up evaluations.

In summary, the limited available evidence regarding the effectiveness of school-based programs that rely on CM for achieving abstinence suggests that this approach combined with cognitive behavioural therapy may yield positive short term (end-of-treatment), but not long term primary cessation outcomes (i.e., abstinence).

5.1.6 Multi-component behavioural interventions

Interventions may increase their efficacy if they concurrently address multiple factors that are empirically known to delay smoking initiation or promote cessation. A few studies have investigated the combined use of "multiple component" or "complex" school-based interventions.[13]

Specifically:

In one US trial assessed the effectiveness of a school-based smoking cessation programme for students caught smoking on school grounds (n=261; mean age 15.8 years).[190] The intervention arm comprised a stage-matched brief phone call intervention that followed up to one year after the completion of a series of four 50-minute sessions of behavioural treatment offered on a monthly basis. The behavioural treatment applied all social influence theory, motivational enhancement, and CBT. Regardless of several study weaknesses (notably, the compulsory nature of participation and the over-reporting of cessation), the study found no differences on biochemically verified 7-day point prevalence cessation rates both at end-of-treatment and at 12-month follow-up between intervention arms.

A study conducted in Germany evaluated the effectiveness of the Losgelöst intervention among 139 adolescents (mean age 14.9 years).[191] The intervention combined CBT and MI offered in 5 group sessions, 1 individual session, and a 4-week aftercare phase. Following the group treatment phase, the participants received 1 phone call and 3 motivational interviewing-based SMS via mobile telephone. A pre-post evaluation found 30% of smokers reported quitting and 38% reduced their cigarette consumption by half. Following the group treatment phase, 24% were self-reported to be abstinent, although the self-reported nature of measuring abstinence weakens the strength of this evidence.

More recently, a Taiwanese trial assessed a 12-week intervention comprising six 45-minute classroom sessions, skill building sessions, self-study materials, coupon-based incentives (motivational enhancement), acupuncture training (alternative medicine), six proactive phone counselling sessions and ten text messages with smoking cessation cues and support.[160] The trial that aimed at strengthening the factors that are known to promote cessation in adolescent smokers involved a total of 143 vocational school students who were randomised to either intervention (n=78) or the educational flyers-only control group (n=65). Bio-chemically-confirmed abstinence rates were significantly higher in the intervention group compared to the control group at end-of-treatment (23% vs. 2%), 1-month (21% vs. 3%), and at 4-month follow-up (21% vs. 2%).

The limited evidence available suggests that multi-component interventions implemented in schools may yield abstinence rates that can reach up to a 4-month post-baseline treatment. These programs may also yield positive short-term secondary cessation outcomes (e.g., reductions in the quantity of cigarettes smoked).

5.1.7 Combined behavioural and pharmacological treatments

The combination of pharmacotherapy and counselling is recommended for supporting cessation in adult populations.[28] School based psychosocial and pharmacological smoking cessation treatments for adolescents as such have been proposed as a potentially effective strategy.[13] Two studies have tested this assumption and have documented non-significant increases in smoking abstinence.

Specifically:

A US trial compared the effectiveness of a standard and an extended duration CBT intervention, involved 141, 17-year-old continuation high school students in an open-label intervention comprising a 10-week CBT group counselling combined with a 9-week NRT.[192] End-of-treatment, biochemically-confirmed data reported a 7-day point prevalence abstinence rate of 14% for the extended treatment group and 7% for the non-extended treatment group, which was non-significant due to sample size (p=0.16).

A French quasi-experimental study involving 943, 17-year-old smokers attending vocational schools in France (n=386 in intervention group and n=557 in control group) compared the effect of four group CBT sessions, individual counselling, and NRT (patch or gum) to standard care control.73 The 30-day-point prevalence abstinence rate at 12-months of follow-up was higher for the intervention than the standard care control condition (11% vs. 7%).

In summary, there is very limited research regarding intervention programs which combine pharmacotherapy and counselling in the school setting.

RECOMMENDATIONS:

- Although limited, there is evidence that brief smoking cessation interventions delivered in school settings that incorporate cognitive behavioural components may be effective in increasing short-term abstinence (Level of Evidence C).
- School-based smoking cessation interventions that are based on cognitive behavioural or motivational enhancement strategies and are delivered over any extended period of time are effective in decreasing daily tobacco consumption and increasing short-term smoking abstinence and should be offered in all school settings (Level of Evidence B).
- There is some evidence that complex interventions which combine intervention approaches (such as school based group counselling with telephone or mobile phone follow-up support, or incentives) may increase abstinence rates up to a 4-months after treatment as well as reductions in cigarettes smoked per day and are recommended as promising practices for intervening with adolescent tobacco users (Level of Evidence C).

6.0
INFORMATION COMMUNICATIONS TECHNOLOGY (ICT)

One of the most recent, emerging trends in smoking cessation programs is the use of computer, web- and mobile phone-based approaches, herewith referred to as information communications technology (ICT). These technologies can serve as useful tools for implementing smoking cessation interventions due to their interactivity as well as their wide reach and ease of use.[193] ICT interventions that have been tested for smoking cessation include: text-message interventions, creating tailored cessation materials based on individual tobacco users data; building flexible learning environments in which participants can interact with "smart" programs or support interaction with other tobacco users.[17, 36-38, 194, 195]

The use of ICT in designing smoking cessation programs seems particularly appropriate for adolescents given the high rates of access to ICT among adolescents. Despite their potential, many challenges remain for optimal development and implementation of ICT-based interventions. In this section, we define ICT interventions as interventions that are either solely delivered through ICT or their main component(s) is/are implemented using ICT.

From 2000 to 2016, 11 studies using ICT approaches were published; four of these were based on stage-based approaches, two on Cognitive Behavioural Therapy (CBT) and, given the lack of strong evidence favoring the use of a single theoretical model, five studies were based on multiple theories. Among the four trials testing the efficacy of solely stage-based ICT interventions, two were computer-based[194, 196] and two used text messaging to participants' mobile phones.[185, 186] All but one study[196] employed a RCT design; two of them were implemented in the US,[194, 196] one in Switzerland[185] and one in China.[186] Although some of the trials showed promising short-term results and reduction in the number of cigarettes smoked per day, none of them yielded significant results in long-term smoking cessation.

Specifically:

Shi (2013)[186] conducted a cluster RCT examining the effectiveness of a 12-week IC intervention compared to an information pamphlet control group among a sample of adolescent weekly smokers in China. The intervention provided TTM stage-matched text messages based on five topic areas:

a) smoking-related health risks,
b) reasonable attitudes towards smoking,
c) ways to initiate a quit attempt,
d) quitting skills, and
e) refusal skills and relapse prevention.

In addition to the text messages, participants were also encouraged to participate in online chatting to support cessation. While there was not a significant intervention effect for 7-day or 30-day point prevalence abstinence at the end of treatment, the intervention condition, relative to the control condition yielded higher rates of smoking reduction (66% vs. 35%) and advancement through quitting stages (52% vs. 18%).

Haug (2013)[185] implemented the "SMS-COACH" programme in Switzerland which tested the efficacy of a 3-month text messaging intervention compared to an assessment-only control group among a sample of 18 year-old daily smokers. The SMS-COACH was based on the Health Access Processes Approach (HAPA) and included an online smoking assessment, weekly text message smoking assessments, tailored text messages, and a quit day relapse prevention text message. At 6-month follow-up, the intervention and control groups did not differ significantly in 7-day point prevalence abstinence (12.5% vs. 9.6%) or 1-month point prevalence abstinence (6.3% vs. 5.5%). However, SMS-COACH participants reduced their cigarette consumption compared to control group participants.

Evers (2012)[194] implemented a RCT to test the efficacy of the "Your Decisions Count– Alcohol, Tobacco and Other Drugs" for Middle Schools, a multi-component TTM-tailored internet-based, computerized intervention program.[213] Ten to 14-year old students in the intervention group were given the opportunity to interact with the computer on three separate occasions, one month apart. The treatment group received up to three, 30-minute internet-based, individualized, interactive intervention sessions, staff and administrator guides, and a parent guide. At the initial 3-month follow-up, the intervention produced significant reductions in the percentage of "ever-smokers" and "current users" who were using tobacco at initial follow-up. However, at the 14-month follow-up, the treatment differences were no longer significant.

A non-randomized pilot trial by Fritz et al. (2008)[196] looked at a computer-based smoking cessation program, to help move smokers along the stages of change.[216] Development of the computerized adolescent smoking cessation program (CASCP) intervention was modelled upon the American Lung Association's "Not on Tobacco" (NOT) program and attempted to follow the stages of change theory. The intervention consisted of four thirty-minute computer sessions and assessments at baseline, post-intervention and one month after. CASCP resulted in an increase in quit attempts ($p=0.05$), lower use of cigarettes ($p=0.049$) and reduced nicotine dependence ($p<.05$) for the intervention group. While the authors report significant results, abstinence was defined as being 1 day smoke-free and as such is a major weakness of the study.

The three ICT interventions that used social cognitive theory were conducted in New Zealand, the US and Taiwan. Specifically:

A trial by Rodgers and colleagues (2005)[197], included 617 adolescent smokers, among a larger sample of 1700 smokers aged 16 years of age or older. Participants received a complex intervention combining social cognitive theory driven elements, based on setting a quit date within 30 days of randomization. They were sent regular, personalized text messages providing smoking cessation advice, support, and distraction with the content covering information relevant to quitting. This included for example, symptoms to expect on quitting, tips to avoid weight gain and improve nutrition, tips to cope with craving. Moreover text messages included advice on avoiding smoking triggers; instructions on breathing exercises to perform instead of smoking; motivational support (for example success stories, feedback on amount of money and life years saved) and distraction (for example, general interest, sports, fashion, trivia, travel). While early results of the interventions were promising (14% vs. 6% ITT at 6-weeks, 29% vs. 19% at 12 weeks), results at 6-month follow-up were non-significant (25% vs. 24%).

Patten and associates (2006)[198] looked at the efficacy of a home-based Internet cessation program (Stomp Out Smokes [SOS], n=70) compared to a clinic-based, brief office intervention (BOI, n = 69). Adolescents assigned to the internet condition had access to the website for 24 weeks and abstinence was assessed at the end of this period. The SOS website resulted in a significantly greater reduction in the average number of smoking days than BOI (p= 0.006), however the smoking abstinence rate at week 24 for SOS was lower (6%) than for the BOI intervention (12%), although this was not statistically significant.

Chen and Yen (2006)[199] compared a smoking cessation group intervention which was combined with an internet-assisted program instruction versus a standard care control group in a 6-week pre-post quasi-experimental design consisting of a total of 77 senior high school adolescents in Taiwan. The intervention comprised an internet-assisted instruction program to provide adolescents with information about the adverse effects of smoking, skills to resist smoking, progress guidance, and relevant online resources for timely help. A cyber discussion forum was also set up and opened to the participants. Participant could share his/her thoughts and feelings in the cessation process and receive peer-to-peer support from other participants, thereby strengthening their willingness to quit smoking. The program condition resulted in a higher reduction in rates of daily smoking (21% reduction versus a 2.5% increase) and a greater number of quit attempts relative to the control group (an average of 1 more quit attempt during the 6-week period). Youth appeared favorable to including the Internet component. However, quit data were not provided in the paper.

Among the five trials that have evaluated interventions built upon multiple theories; four of these[172, 200-202] were implemented in the US and one[193] in Canada. Some of the interventions yielded promising results, though not biochemically confirmed and retained for longer than a few weeks or months of follow-up. Moreover the variety in design and theoretical background among interventions makes it impossible to clarify which, if any, are the most promising component combinations in terms of future interventions for adolescent smoking cessation.

Specifically:

Peterson et al. (2009)[172] examined the use of a telephone-delivered Motivational Interviewing (MI) intervention combined with a Transtheoretical Model of Change (TTM)-based website. Fifty high schools in Washington State (USA) were randomly assigned to either the phone/website intervention (n=25 schools; n=1,058) or no-intervention control condition (n=25 schools; n=1,093). Adolescent monthly smokers in the phone intervention group, initially received 5-minutes of telephone counseling to quit smoking. At this time, adolescents who were not motivated to quit received up to 3 consecutive phone sessions. If adolescents were initially motivated to quit or became motivated to quit after the 3 sessions, they received up to 6 consecutive sessions. The intervention also included school-based print and electronic media campaign against tobacco. Intervention participants, when compared with the control group, had significantly higher self-reported seven-day (47.5% vs. 40.0%), one-month (35.5% vs. 28.7%), and 6-month (21.8% vs. 17.7%) prolonged abstinence rates. However, abstinence was not confirmed biochemically.

Woodruff et al. (2007)[202] randomized high-school students to either a Web-based virtual reality world based on motivational interviewing and cognitive theory or a measurement-only control group. Participants in the intervention group were asked to spend 45 minutes per week in a virtual reality world with other teenagers and a counselor to explore smoking. Information was presented within "shops" and "galleries"; chatting was also possible as more than one student could be online. In addition to the web-based intervention, students were also offered one-to-one counseling sessions with smoking cessation professional. Immediately following the intervention, the intervention group had higher rates of 7-day absti¬nence than the control condition (35% vs. 22%; $p<0.01$). However, at 12 months follow-up, there was no difference between the two groups (39% vs. 38%; $p>0.05$).

An intervention in Canada used the internet as assistance targeted both the prevention and cessation of tobacco use among adolescents.[193] A combination of the Internet, paper journals, a single group based motivational interviewing comprised the program, and follow-up e-mails for six months were utilized to prevent smoking initiation for non-smokers and cessation for the ones already smoking. Paper journals were used to record assessment scores, which were further discussed at a small group 10-minute motivational interview. Monthly e-mails tailored to the individual based on assessment scores were sent for six months post intervention. Likelihood of high intention to smoke was reduced ($p<.05$) while increased likelihood of high resistance to cigarette use ($p<.05$) was recorded at the 6-month follow up in the intervention group.

Lipkus (2004)[200] used a TTM-based intervention that also included motivational enhancement via telephone and cognitive behavioural therapy (CBT) for young people recruited in the community (shopping malls and an amusement park). At the eight-month follow-up, no significant effect on seven-day point prevalence abstinence was found (RR 1.10, 95% CI 0.74 to 1.62).

Prokhorov et al. (2008)[201] evaluated a computer-assisted, counsellor-delivered smoking cessation programme

founded on Social Cognitive theory and the Transtheoretical Model of Change.The Smoking Prevention Interactive Experience (ASPIRE) curriculum contained embedded animations, video, and interactive activities. It was composed of five weekly sessions in one semester and two "booster" sessions in the following semester (each 30 min in duration) accessed on a desktop computer in the classroom during lesson periods. Overall, ASPIRE featured eight educational "tracks" (over 5-hours of videos, animations, interactive quizzes, etc.) and was designed to address the needs of both smokers and non-smokers. Significant differences for smoking cessation were not found for either group ($p>.05$) at the 18-month follow-up assessments. However, participants in the intervention had higher decisional balance, and reduced temptation to smoke ($p<.05$).

In summary, while ICT interventions are promising strategies for addressing tobacco use in adolescents, data supporting the effectiveness of ICT-based interventions is still limited and as such it is recommended that they be used in combination with counselling.

RECOMMENDATIONS:

- Information communication technology (ICT) interventions are an effective strategy for decreasing daily tobacco use in adolescents, however available evidence cannot support the use of ICT in supporting long-term smoking cessation, as such it is recommended information technology interventions be used in combination with other counselling based intervention strategies (Level of Evidence B).

7.0
OTHER COMMUNITY SETTINGS

Apart from health care facilities, school settings and ICT, smoking cessation interventions can be implemented in community settings reaching, in some cases, populations who cannot be reached elsewhere. Research suggests that multiple social, psychosocial (perceptions, knowledge, intentions), and environmental determinants influence the onset and progression of smoking during adolescence. As such, community-level influences together with other settings can lead to higher or lower prevalence of smoking among adolescents.[203, 204]

From 2000-1016, three trials on adolescent smoking cessation have evaluated interventions implemented solely within community settings. Two studies used mainly Cognitive Behavioral approaches; one was employed in summer camps in Russia,[205] and villages of Native Americans in Alaska,[206] and the third was an open-label study evaluating the effect of a nationwide smoking Quitline in South Korea.[207]

Specifically:

Idrisov et al. (2013)[205] compared the Project Ex Programme with standard care control group among adolescent monthly smokers (n=164) attending summer recreational camps in Russia (mean age = 16.7 years). The curriculum of Project Ex was built upon Cognitive Behavioral and MI techniques and involved the use of four talk show enactments of different smoking cessation issues, four alternative medicine techniques ("healthy breathing", "yoga activity", "letting feelings pass" meditation activity, and a "relaxation activity"), a homework assignment in which smokers notice the effects of cigarette smoking on them, a competitive game about passive smoking ("is smoking on the menu?"), and tobacco consequences, and quit and maintenance strategies (e.g., coping). The program was delivered in a group format using enjoyable and motivating games and activities. At the 6-month follow-up, intervention participants reported higher rates of 30-day abstinence compared to the control group (7.5% vs. 0.1%). Additionally, nicotine dependence was reduced among those who had not quit in the intervention condition at the 6-month follow-up. Though promising, the results of the intervention may be overestimated, as there was no biochemical verification of cessation. Additionally Project-EX participants received more consistent encouragement to quit from camp counsellors in addition to the program sessions.

Patten and colleagues (2014)[206] evaluated a cognitive behavioral therapy-based intervention in Alaskan Na-

tive adolescent smokers in the USA. The intervention was group-based and included talking circles, personal stories from elders and recreational activities. The intervention group did not differ significantly from the control group on 7-day self-reported point prevalence of tobacco abstinence at end of treatment and at 6-month follow-up. However, at the end of treatment, participants in the intervention group reported reduced frequency of tobacco use compared to baseline.

Lim and colleagues (2012)[207] evaluated the effectiveness of a Quitline among adolescent smokers (aged 13-19 years), as well as other factors associated with adolescent smoking cessation in the Republic of Korea. The observational study involved 642 adolescent Quitline users who were offered systematic and comprehensive behavioral counseling based on the Transtheoretical Model of Change over a one-year period. The intervention included seven telephone calls during the first 30 days and 14 additional calls over the next 11 months for smoking cessation and maintenance. The coaching and communication protocol used was tailored to adolescent tobacco users. Booklets and SMS messages were also delivered throughout the cessation process. At the 6-month follow-up, 13.4% of boys and 6.6% of girls reported that they had quit smoking.

In summary, there is some limited evidence suggesting that community settings, such as summer camps or neighbourhood recreation centres, should be considered for the implementation of smoking cessation interventions in adolescents.

RECOMMENDATIONS:

- Community settings, such as summer camps or neighbourhood recreation centres, should be considered for the implementation of smoking cessation interventions in adolescents (Level of Evidence C).

APPENDIX A – Key recommendations in existing Guidelines

GUIDELINE	SUMMARY STATEMENT
Australia - Royal Australian College of General Practitioners (2011)[57]	– Counselling is considered to be vital in this age group. – Health professionals should ask about smoking and provide a strong anti-smoking message. – NRT is recommended to adolescents only with precautions. The health professional should assess the nicotine dependence, motivation to quit and willingness to accept counselling before recommending NRT. – Bupropion and varenicline are not approved for use by smokers under 18 years of age.
Canada - CAN-ADAPTT (2011)[51]	– Health care providers, who work with youth (children and adolescents), should obtain information about tobacco use (cigarettes, cigarillos, water pipe, etc.) on a regular basis. (Grade: 1A) – Health care providers are encouraged to provide counselling that supports abstinence from tobacco and/or cessation to youth (children and adolescents) that use tobacco. (Grade: 2C) – Health care providers in paediatric health care settings should counsel parents/guardians about the potential harmful effects of second-hand smoke on the health of their children. (Grade: 2C)
Canada - Canadian Paediatric Society (2016)[11]	– See table below.
United Kingdom - National Institute for Health and Clinical Excellence (NICE) Guidelines (2008)[55]	– Recommend nicotine replacement therapy coupled with behavioural interventions for patients with nicotine dependence beginning at age 12 years. – Careful consideration of risks and benefits should be employed by the provider and explained to the patient and the legal guardian. – Do not recommend the use of varenicline or bupropion for tobacco users younger than 18 years.

GUIDELINE	SUMMARY STATEMENT
USA - US-Preventive-Services-Task-Force (2013)[208, 209]	– Clinicians should establish tobacco use status for all patients and reassess at every opportunity. All forms of tobacco should be included in this assessment. Clinicians should recommend on-going cessation services to all tobacco users at every opportunity and reinforce non-users to continue avoiding tobacco products (Strong Recommendation), U.S. Preventive Services Task Force [Low Quality Evidence]. – Counselling messages for effective shared decision-making, for children and adolescents using tobacco include: • Emphasize short-term negative effects of tobacco use. • Advise tobacco users to quit. • Assess user's willingness to make a quit attempt. • Provide a motivational intervention if the user is not ready to make a quit effort. • Assist in quitting if ready to make a quit effort. Negotiate a quit date. Counsel to support cessation and build abstinence skills. Offer phone line for more assistance. • Arrange follow-up to occur soon after the quit date • Provide educational and self-help materials for all patients and families • Support school and family based programs to help prevent smoking
USA - 2008 Clinical Practice Guidelines on the Treatment of Tobacco Use and Dependence[28]	– There great potential of counselling and brief advice in aiding adolescents to quit smoking. – Due to a lack of strong evidence about its effectiveness (Strength of Evidence = C), for bupropion SR or nicotine replacement therapy are not recommended for adolescent smokers when there was evidence of nicotine dependence and desire to quit tobacco use.

GUIDELINE	SUMMARY STATEMENT
New Zealand:- Ministry of Health[54]	– There is insufficient evidence to confirm the effectiveness of interventions specifically aimed at helping young people stop smoking, or to recommend integrating any particular models into standard practice. – It is likely that, to be effective, interventions aimed at young people need to differ from those developed for adults, given that these two groups differ in lifestyle and in attitudes to smoking and stopping smoking. Interventions that may be acceptable for young people who smoke include support from family, friends and community, incentives, physical activity and group support. – There is insufficient evidence to state that using NRT improves long-term abstinence rates among young smokers. Nevertheless, expert opinion is that NRT may be considered for use by young people who want help to stop smoking. – Health care workers should be aware of the risks of second-hand smoke to children and young people exposed to smoking by their families in their homes. On these grounds alone, health care workers should offer brief advice and cessation support to family members who smoke. **RECOMMENDATIONS:** • Offer stop-smoking interventions that incorporate components known to be effective (such as those identified in the previous sections) to young people who smoke. [Grade ✓] • Young people (aged 12–18 years) who are dependent on nicotine can use NRT if it might help them stop smoking. [Grade C]

Canadian Paediatric Society [11] - Summary of smoking cessation interventions in youth:

INTERVENTION	RECOMMENDED/NOT RECOMMENDED	LEVEL OF EVIDENCE
Brief counselling (in person: individual or group)	Recommended	1b
Cognitive behavioural therapy	Recommended	1b
Phone or distance counselling	Recommended	2b
Mobile phone interventions (text messages reminders from health care providers)	Recommended in combination with other interventions	2b
Self-help, non-interactive audio-visual materials	Recommended in combination with other interventions	3b
Nicotine replacement product (gums, patches, lozenges, sprays)	Recommended only for regular smokers 12 to 18 years of age	3b
Bupropion	Recommended in some cases, use with caution	5
Varenicline	Recommended in some cases, use with caution	5
E-cigarettes	Not Recommended	4
Other pharmaceuticals: clonidine, nortriptyline, and cytisine	Insufficient Evidence	-
Internet and social media base interventions	Insufficient Evidence	-
School-bade cessation programs	Insufficient Evidence	-
Mind-body therapies and hypnosis	Insufficient Evidence	-

REFERENCES

1. Sims TH. The Committee on Substance Abuse. Technical Report—Tobacco as a substance of abuse. Pediatrics. 2009;124:e1045-53.
2. Kraus L, Guttormsson U, Leifman H, Arpa S, Molinaro S, Monshouwer K, et al. ESPAD Report 2015 - Results from the European School Survey Project on Alcohol and Other Drugs. Luxembourg: European School Survey Project on Alcohol and Other Drugs2016.
3. European Commission. Special Euroberometer 429. Attitudes of Europeans toward tobacco and electronic cigarettes: European Commission, Directorate-General for Health and Food Safety. May 2015.
4. Fidler J, Wardle J, Brodersen NH, Jarvis M, West R. Vulnerability to smoking after trying a single cigarette can lie dormant for three years or more. Tob Control. 2006;15(3):205-9.
5. Palmer R, Young S, Hopfer C, Corley R, Stallings M, Crowley T, et al. Developmental epidemiology of drug use and abuse in adolescence and young adulthood: Evidence of generalized risk. Drug Alcohol Depend. 2009;102(1):78-87.
6. U.S. Department of Health and Human Services. E-Cigarette Use Among Youth and Young Adults. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health https://e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Full_Report_non-508.pdf2016.
7. Branstetter SA, Horn K, Dino G, Zhang J. Beyond quitting: Predictors of teen smoking cessation, reduction and acceleration following a school-based intervention. Drug Alcohol Depend. 2009;99(1-3):160-8.
8. Stanton W, Baade P, Moffatt J. Predictors of smoking cessation processes among secondary school students. Subst Use Misuse. 2006;41(13):1683-94.
9. Balch GI, Tworek C, Barker DC, Sasso B, Mermelstein RJ, Giovino GA. Opportunities for youth smoking cessation: findings from a national focus group study. Nicotine and Tobacco Research. 2004;6(1):9-17.
10. Ellickson PL, Tucker JS, Klein DJ. Sex differences in predictors of adolescent smoking cessation. Health Psychol. 2001;20(3):186-95.
11. Harvey J, Chadi N. Strategies to promote smoking cessation among adolescents. Paediatrics & Child Health. 2016;21(4):201-8.
12. Sussman S. Effects of sixty six adolescent tobacco use cessation trials and seventeen prospective studies of self-initiated quitting. Tob Induc Dis. 2002;1(1):35-81.
13. Stanton A, Grimshaw G. Tobacco cessation interventions for young people. Cochrane Database Syst Rev. 2013(8):10.1002/14651858.CD003289.pub5.
14. Simon P, Kong G, Cavallo D, Krishnan-Sarin

S. Update of adolescent smoking cessation interventions: 2009–2014. Current Addiction Reports. 2015;2(1):15-23.
15. Pbert L, Farber H, Horn K, Lando HA, Muramoto M, O'Loughlin J, et al. State-of-the-art office-based interventions to eliminate youth tobacco use: the past decade. Pediatrics. 2015;135(4):734-47.
16. Canadian Paediatric Society. Recommendations on behavioural interventions for the prevention and treatment of cigarette smoking among school-aged children and youth. CMAJ. 2017;189:E310-6.
17. Gabble R, Babayan A, DiSante E, Schwartz R. Smoking Cessation Interventions for Youth: A Review of the Literature. Toronto: Ontario Tobacco Research UnitFebruary 2015.
18. Milton M, Maule C, Yee S, Backinger C, Malarcher A, Husten C. Youth Tobacco Cessation: A Guide for Making Informed Decisions. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention2004.
19. Latimer AE, Krishnan-Sarin S, Cavallo DA, Duhig A, Salovey P, O'Malley SA. Targeted smoking cessation messages for adolescents. J Adolesc Health. 2012;50(1):47-53.
20. Hanson K, Allen S, Jensen S, Hatsukami D. Treatment of adolescent smokers with the nicotine patch. Nicotine and Tobacco Research. 2003;5(4):515-26.
21. Roddy E, Romilly N, Challenger A, Lewis S, Britton J. Use of nicotine replacement therapy in socioeconomically deprived young smokers: a community-based pilot randomised controlled trial. Tob Control. 2006;15(5):373-6.
22. Hurt RD, Croghan GA, Beede SD, Wolter TD, Croghan IT, Patten CA. Nicotine patch therapy in 101 adolescent smokers: efficacy, withdrawal symptom relief, and carbon monoxide and plasma cotinine levels. Arch Pediatr Adolesc Med. 2000;154(1):31-7.
23. Killen JD, Ammerman S, Rojas N, Varady J, Haydel F, Robinson TN. Do adolescent smokers experience withdrawal effects when deprived of nicotine? Experimental and Clinical Psychopharmacology. 2001;9(2):176-82.
24. Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, et al. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics. 2005;115(4):e407-e14.
25. Scherphof CS, van den Eijnden RJJM, Engels RCME, Vollebergh WAM. Short-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: A randomized controlled trial. J Subst Abuse Treat. 2014;46(2):120-7.
26. Scherphof CS, van den Eijnden RJJM, Engels RCME, Vollebergh WAM. Long-term efficacy of nicotine replacement therapy for smoking cessation in adolescents: A randomized controlled trial. Drug Alcohol Depend.

REFERENCES

2014;140:217-20.

27. Berra S, Tebé C, Erhart M, Ravens-Sieberer U, Auquier P, Detmar S, et al. Correlates of use of health care services by children and adolescents from 11 European countries. Med Care. 2009;47(2):161-7.
28. Fiore MC, Jaén CR, Baker TB, et al. Clinical Practice Guideline - Treating Tobacco Use and Dependence: 2008 Update. Rockville, MD: U.S. Department of Health and Human Services2008.
29. European Network for Smoking and Tobacco Prevention [ENSP]. European Smoking Cessation Guidelines. Brussels: European Network for Smoking and Tobacco Prevention (ENSP)2012.
30. Price JH, Yingling F, Dake JA, Telljohann SK. Adolescent smoking cessation services of school-based health centers. Health Educ Behav. 2003;30(2):196-208.
31. Sussman S, Sun P, Dent CW. A meta-analysis of teen cigarette smoking cessation. Health Psychol. 2006;25(5):549.
32. Sussman S, Sun P. Youth tobacco use cessation: 2008 update. Tobacco Induced Diseases. 2009;5(1):3-.
33. Sussman S, Dent CW, Lichtman KL. Project EX. Outcomes of a teen smoking cessation program. Addict Behav. 2001;26(3):425-38.
34. Sussman S, McCuller WJ, Zheng H, Pfingston YM, Miyano J, Dent CW. Project EX: A Program of Empirical Research on Adolescent Tobacco Use Cessation. Tob Induc Dis. 2004;2(3):119-32.
35. Sun P, Miyano J, Rohrbach LA, Dent CW, Sussman S. Short-term effects of Project EX-4: A classroom-based smoking prevention and cessation intervention program. Addict Behav. 2007;32(2):342-50.
36. Mason M, Ola B, Zaharakis N, Zhang J. Text messaging interventions for adolescent and young adult substance use: a meta-analysis. Prevention Science. 2015;16(2):181-8.
37. Park E, Drake E. Systematic review: internet-based program for youth smoking prevention and cessation. Journal of Nursing Scholarship. 2015;47(1):43-50.
38. Civljak M, Stead LF, Hartmann-Boyce J, Sheikh A, Car J. Internet-based interventions for smoking cessation. The Cochrane Library. 2013(7):10.1002/14651858.CD007078.pub4.
39. Lewit EM, Hyland A, Kerrebrock N, Cummings KM. Price, public policy, and smoking in young people. Tob Control. 1997;6(suppl 2):S17.
40. Guindon GE, Tobin S, Yach D. Trends and affordability of cigarette prices: ample room for tax increases and related health gains. Tob Control. 2002;11(1):35-43.
41. Levy DT, Chaloupka F, Gitchell J. The effects of tobacco control policies on smoking rates: a tobacco control scorecard. J Public Health Manag Pract. 2004;10(4):338-53.
42. Liang L, Chaloupka F, Nichter M, Clayton R.

Prices, policies and youth smoking, May 2001. Addiction. 2003;98(1):105-22.
43. Lovato C, Watts A, Stead LF. Impact of tobacco advertising and promotion on increasing adolescent smoking behaviours. The Cochrane Library. 2011(10):10.1002/14651858.CD003439.pub2.
44. Chen V, Forster JL. The long-term effect of local policies to restrict retail sale of tobacco to youth. Nicotine & Tobacco Research. 2006;8(3):371-7.
45. Johnston LD, Miech RA, O'Malley PM, Bachman JG, Schulenberg JE. Use of Ecstasy, Heroin, Synthetic Marijuana, Alcohol, Cigarettes Declined Among US teens in 2015. Ann Arbor: University of Michigan News Service2015.
46. Office for National Statistics-Social and Vital Statistics Division. General Lifestyle Survey, 2011: Special Licence Access. [data collection]. UK Data Service. SN: 7475, http://dx.doi.org/10.5255/UKDA-SN-7475-1. 2014.
47. Arday DR, Giovino GA, Schulman J, Nelson DE, Mowery P, Samet JM. Cigarette smoking and self-reported health problems among US high school seniors, 1982-1989. Am J Health Promot. 1995;10(2):111-6.
48. Arnett JJ. Optimistic bias in adolescent and adult smokers and nonsmokers. Addict Behav. 2000;25(4):625-32.
49. Tworek C, Schauer GL, Wu CC, Malarcher AM, Jackson KJ, Hoffman AC. Youth tobacco cessation: quitting intentions and past-year quit attempts. Am J Prev Med. 2014;47(2):S15-S27.
50. Bachmann MS, Znoj H, Brodbeck J. Smoking behaviour, former quit attempts and intention to quit in urban adolescents and young adults: a five-year longitudinal study. Public Health. 2012;126(12):1044-50.
51. CAN-ADAPTT. Canadian Smoking Cessation Guideline Version 2.0: Specific Populations: Youth (Children and Adolescents)March 31, 2011.
52. Committee on Environmental Health; Committee on Substance Abuse; Committee on Adolescence and Committee on Native American Child Health. From the American Academy of Pediatrics: policy statement—tobacco use: a pediatric disease. Pediatrics. 2009;124(5):1474-87.
53. McRobbie H, Bullen C, Glover M, Whittaker R, Wallace-Bell M, Fraser T. New Zealand smoking cessation guidelines. NZ Med J. 2008;121(1276):57-70.
54. Ministry of Health. Background and Recommendations of the New Zealand Guidelines for Helping People to Stop Smoking. Wellington: Ministry of Health2014.
55. National Institute for Health and Clinical Excellence (NICE). Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities. London (UK): NICE2008.

REFERENCES

56. Wilkinson P, Kelvin R, Roberts C, Dubicka B, Goodyer I. Clinical and Psychosocial Predictors of Suicide Attempts and Nonsuicidal Self-Injury in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT). AJ Psychiatry. 2011;168(5):495-501.
57. Zwar N, Richmond R, Borland R, Peters M, Litt J, Bell J, et al. Supporting Smoking Cessation: a Guide for Health Professionals. Melbourne: The Royal Australian College of General Practitioners2011 (updated 2014).
58. Leatherdale ST. What modifiable factors are associated with cessation intentions among smoking youth? Addict Behav. 2008;33(1):217-23.
59. McCuller WJ, Sussman S, Wapner M, Dent C, Weiss DJ. Motivation to quit as a mediator of tobacco cessation among at-risk youth. Addict Behav. 2006;31(5):880-8.
60. White A, Editorial Board of Acupuncture in Medicine. Western medical acupuncture: a definition. Acupuncture in Medicine. 2009;27(1):33.
61. Chenoweth MJ, O'Loughlin J, Sylvestre M-P, Tyndale RF. CYP2A6 slow nicotine metabolism is associated with increased quitting by adolescent smokers. Pharmacogenetics and Genomics. 2013;23(4):232.
62. Dijk F, Reubsaet A, de Nooijer J, de Vries H. Smoking status and peer support as the main predictors of smoking cessation in adolescents from six European countries. Nicotine and Tobacco Research. 2007;9(SUPPL. 3):S495-S504.
63. Grimshaw G, Stanton A, Blackburn C, Andrews K, Grimshaw C, Vinogradova Ye, et al. Patterns of smoking, quit attempts and services for a cohort of 15-to 19-year-olds. Child Care Health Dev. 2003;29(6):457-64.
64. Riedel BW, Robinson LA, Klesges RC, McLain-Allen B. Characteristics of adolescents caught with cigarettes at school: implications for developing smoking cessation programs. Nicotine Tob Res. 2002;4(3):351-4.
65. O'Loughlin JL, Sylvestre M-P, Dugas EN, Karp I. Predictors of the occurrence of smoking discontinuation in novice adolescent smokers. Cancer Epidemiology and Prevention Biomarkers. 2014;23(6):1090-101.
66. Haug S, Schaub MP, Schmid H. Predictors of adolescent smoking cessation and smoking reduction. Patient Educ Couns. 2014;95(3):378-83.
67. Vuckovic N, Polen MR, Hollis JF. The problem is getting us to stop: What teens say about smoking cessation. Prev Med. 2003;37(3):209-18.
68. Hu M-C, Muthén B, Schaffran C, Griesler PC, Kandel DB. Developmental trajectories of criteria of nicotine dependence in adolescence. Drug Alcohol Depend. 2008;98(1):94-104.
69. Kleinjan M, Engels RC, van Leeuwe J, Brug J, van Zundert RM, van den Eijnden RJ. Mechanisms of adolescent smoking cessation:

roles of readiness to quit, nicotine dependence, and smoking of parents and peers. Drug Alcohol Depend. 2009;99(1-3):204-14.
70. Van Zundert RMP, Boogerd EA, Vermulst AA, Engels RCME. Nicotine withdrawal symptoms following a quit attempt: An ecological momentary assessment study among adolescents. Nicotine and Tobacco Research. 2009;11(6):722-9.
71. Curry SJ, Mermelstein RJ, Sporer AK. Therapy for specific problems: youth tobacco cessation. Annu Rev Psychol. 2009;60:229.
72. Fritz DJ, Wider LC, Hardin SB, Horrocks M. Program strategies for adolescent smoking cessation. The Journal of school nursing : the official publication of the National Association of School Nurses. 2008;24(1):21-7.
73. Minary L, Cambon L, Martini H, Wirth N, Acouetey DS, Thouvenot F, et al. Efficacy of a smoking cessation program in a population of adolescent smokers in vocational schools: A public health evaluative controlled study. BMC Public Health. 2013;13(1).
74. Lane NE, Leatherdale ST, Ahmed R. Use of nicotine replacement therapy among Canadian youth: data from the 2006–2007 national youth smoking survey. Nicotine & Tobacco Research. 2011:ntr091.
75. World Health Organization [WHO]. History of the WHO Framework Convention on Tobacco Control. Switzerland: World Health Organization; 2009.
76. Main C, Thomas S, Ogilvie D, Stirk L, Petticrew M, Whitehead M, et al. Population tobacco control interventions and their effects on social inequalities in smoking: placing an equity lens on existing systematic reviews. BMC Public Health. 2008;8(1):178.
77. Wilson LM, Avila Tang E, Chander G, Hutton HE, Odelola OA, Elf JL, et al. Impact of tobacco control interventions on smoking initiation, cessation, and prevalence: a systematic review. Journal of Environmental and Public Health. 2012;961724:doi: 10.1155/2012/961724.
78. Hublet A, Schmid H, Clays E, Godeau E, Gabhainn SN, Joossens L, et al. Association between tobacco control policies and smoking behaviour among adolescents in 29 European countries. Addiction. 2009;104(11):1918-26.
79. White VM, Warne CD, Spittal MJ, Durkin S, Purcell K, Wakefield MA. What impact have tobacco control policies, cigarette price and tobacco control program funding had on Australian adolescents' smoking? Findings over a 15-year period. Addiction. 2011;106(8):1493-502.
80. Jha P, Chaloupka FJ. Curbing the Epidemic: Governments and the Economics of Tobacco Control: World Bank Publications; 1999.
81. Slater SJ, Chaloupka FJ, Wakefield M, Johnston LD, O'Malley PM. The impact of retail cigarette marketing practices on youth smoking uptake. Arch Pediatr Adolesc Med. 2007;161(5):440-5.

REFERENCES

82. Pförtner T-K, Hublet A, Schnohr CW, Rathmann K, Moor I, de Looze M, et al. Socioeconomic inequalities in the impact of tobacco control policies on adolescent smoking. A multilevel study in 29 European countries. Addict Behav. 2016;53:58-66.
83. Wakefield MA, Chaloupka FJ, Kaufman NJ, Orleans CT, Barker DC, Ruel EE. Effect of restrictions on smoking at home, at school, and in public places on teenage smoking: cross sectional study. BMJ. 2000;321(7257):333-7.
84. Brin M, Carson K, Esterman A, Chang A, BJ. S. Mass media interventions for preventing smoking in young people. Cochrane Database Syst Rev. 2010(11):10.1002/14651858. CD001006.pub2.
85. Chaloupka FJ. Macro-social influences: the effects of prices and tobacco-control policies on the demand for tobacco products. Nicotine & Tobacco Research. 1999;1(Suppl 2):S77-S81.
86. Emery S, Wakefield MA, Terry-McElrath Y, Saffer H, Szczypka G, O'Malley PM, et al. Televised state-sponsored antitobacco advertising and youth smoking beliefs and behavior in the United States, 1999-2000. Arch Pediatr Adolesc Med. 2005;159(7):639-45.
87. Goldberg ME, Liefeld J, Madill J, Vredenburg H. The effect of plain packaging on response to health warnings. Am J Public Health. 1999;89(9):1434-5.
88. British Medical Association. Doctors back cigarette ban to those born after 2000: Available at: http://bma.org.uk/news-views-analysis/news/2014/june/doctors-back-cigarette-ban-to-those-born-after-20002014 (June 24).
89. Khoo D, Chiam Y, Ng P, Berrick AJ, Koong H. Phasing-out tobacco: proposal to deny access to tobacco for those born from 2000. Tob Control. 2010;19(5):355-60.
90. McDaniel PA, Smith EA, Malone RE. The tobacco endgame: a qualitative review and synthesis. Tob Control. 2015:tobaccocontrol-2015-052356.
91. Henry-Edwards S, Humeniuk R, Ali R, Monteiro M, Poznyak V. Brief intervention for substance use: A manual for use in primary care. World Health Organization. 2003.
92. Price JH, Jordan TR, Dake JA. Pediatricians' use of the 5 A's and nicotine replacement therapy with adolescent smokers. J Community Health. 2007;32(2):85-101.
93. West R, Raw M, McNeill A, Stead L, Aveyard P, Bitton J, et al. Health-care interventions to promote and assist tobacco cessation: a review of efficacy, effectiveness and affordability for use in national guideline development. Addiction (Abingdon, England). 2015;110(9):1388-403.
94. Center for Substance Abuse Treatment. Brief Interventions and Brief Therapies for Substance Abuse. Treatment Improvement Protocol (TIP) Series 34. (DHHS Publication No. SMA 03-3810). Rockville, MD: U.S.

Department of Health and Human Services, Substance Abuse and Mental Health Services Administration. 2012.
95. Miller W, Rollnick S. Motivational Interviewing: Preparing People for Change. 2nd The Guilford Press. New York. 2002.
96. MacGowan MJ, Engle B. Evidence for optimism: Behavior therapies and motivational interviewing in adolescent substance abuse treatment. Child Adolesc Psychiatr Clin N Am. 2010;19(3):527-45.
97. Barnett E, Sussman S, Smith C, Rohrbach LA, Spruijt-Metz D. Motivational Interviewing for adolescent substance use: a review of the literature. Addict Behav. 2012;37(12):1325-34.
98. Bandura A. Health promotion by social cognitive means. Health Educ Behav. 2004;31(2):143-64.
99. Prochaska J, DiClemente C. Self change processes, self efficacy and decisional balance across five stages of smoking cessation. Prog Clin Biol Res. 1984;156:131-40.
100. Prochaska JO, DiClemente CC, Norcross JC. In search of how people change: applications to addictive behaviors. Am Psychol. 1992;47(9):1102-14.
101. Stanger C, Budney AJ. Contingency management approaches for adolescent substance use disorders. Child Adolesc Psychiatr Clin N Am. 2010;19(3):547-62.
102. Sigmon SC, Patrick ME. The use of financial incentives in promoting smoking cessation. Prev Med. 2012;55:S24-S32.
103. Tidey JW. Using incentives to reduce substance use and other health risk behaviors among people with serious mental illness. Prev Med. 2012;55:S54-S60.
104. Krishnan-Sarin S, Cavallo DA, Cooney JL, Schepis TS, Kong G, Liss TB, et al. An exploratory randomized controlled trial of a novel high-school-based smoking cessation intervention for adolescent smokers using abstinence–contingent incentives and cognitive behavioral therapy. Drug Alcohol Depend. 2013;132(1):346-51.
105. McDonald P, Colwell B, Backinger CL, Husten C, Maule CO. Better practices for youth tobacco cessation: evidence of review panel. Am J Health Behav. 2003;27 Suppl 2:S144-58.
106. European Medicines Agency [EMA]. Bupropion hydrochloride. [16/11/2015]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Bupropion_hydrochloride/human_referral_000110.jsp.
107. Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA. 2006;296(1):64-71.
108. Hanson K, Zylla E, Allen S, Li Z, Hatsukami DK. Cigarette reduction: an intervention for adolescent smokers. Drug Alcohol Depend. 2008;95(1-2):164-8.

REFERENCES

109. Smith TA, House RF, Croghan IT, Gauvin TR, Colligan RC, Offord KP, et al. Nicotine patch therapy in adolescent smokers. Pediatrics. 1996;98(4):659-67.
110. Lemmens V, Oenema A, Knut IK, Brug J. Effectiveness of smoking cessation interventions among adults: a systematic review of reviews. Eur J Cancer Prev. 2008;17(6):535-44.
111. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, et al. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2012(11):10.1002/14651858.CD000146.pub4.
112. Jacobsen LK, Krystal JH, Mencl WE, Westerveld M, Frost SJ, Pugh KR. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. Biol Psychiatry. 2005;57(1):56-66.
113. Swanson AN, Shoptaw S, Heinzerling KG, Wade AC, Worley M, McCracken J, et al. Up in smoke? A Preliminary open-label trial of nicotine replacement therapy and cognitive behavioral motivational enhancement for smoking cessation among youth in Los Angeles. Subst Use Misuse. 2013;48(14):1553-62.
114. Rubinstein ML, Benowitz NL, Auerback GM, Moscicki A-B. A randomized trial of nicotine nasal spray in adolescent smokers. Pediatrics. 2008;122(3):e595-e600.
115. Bailey SR, Crew EE, Riske EC, Ammerman S, Robinson TN, Killen JD. Efficacy and tolerability of pharmacotherapies to aid smoking cessation in adolescents. Pediatric Drugs. 2012;14(2):91-108.
116. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013(5):10.1002/14651858.CD009329.pub2.
117. Gray KM, Carpenter MJ, Baker NL, Hartwell KJ, Lewis AL, Hiott DW, et al. Bupropion SR and contingency management for adolescent smoking cessation. J Subst Abuse Treat. 2011;40(1):77-86.
118. Gray KM, Carpenter MJ, Lewis AL, Klintworth EM, Upadhyaya HP. Varenicline versus bupropion XL for smoking cessation in older adolescents: A randomized, double-blind pilot trial. Nicotine and Tobacco Research. 2012;14(2):234-9.
119. Killen JD, Robinson TN, Ammerman S, Hayward C, Rogers J, Stone C, et al. Randomized clinical trial of the efficacy of bupropion combined with nicotine patch in the treatment of adolescent smokers. J Consult Clin Psychol. 2004;72(4):729-35.
120. Muramoto ML, Leischow SJ, Sherrill D, Matthews E, Strayer LJ. Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. Arch Pediatr Adolesc Med. 2007;161(11):1068-74.

121. Niederhofer H, Huber M. Bupropion may support psychosocial treatment of nicotine-dependent adolescents: Preliminary results. Pharmacotherapy. 2004;24(11):1524-8.
122. Upadhyaya HP, Brady KT, Wang W. Bupropion SR in adolescents with comorbid ADHD and nicotine dependence: a pilot study. J Am Acad Child Adolesc Psychiatry. 2004;43(2):199-205.
123. Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med. 1999;340(9):685-91.
124. Kim Y, Myung SK, Jeon YJ, Lee EH, Park CH, Seo HG, et al. Effectiveness of pharmacologic therapy for smoking cessation in adolescent smokers: Meta-analysis of randomized controlled trials. Am J Health Syst Pharm. 2011;68(3):219-26.
125. Gonzales D, Rennard S, Nides M, Oncken C, Azoulay S, Billing C, et al. Varenicline Phase 3 Study Group: Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006;296(1):47-55.
126. Faessel H, Ravva P, Williams K. Pharmacokinetics, safety, and tolerability of varenicline in healthy adolescent smokers: A multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther. 2009;31(1):177-89.
127. Pfizer. Smoking cessation study in healthy adolescent smokers. http://clinicaltrials.gov/ct2/ (accessed 18/10/2015); Vol. Clinical Trials.gov ID NCT013129092011.
128. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2012;Issue 4:CD006103. DOI: 10.1002/14651858.CD006103.pub6.
129. White AR, Rampes H, Liu JP, Stead LF, Campbell J. Acupuncture and related interventions for smoking cessation. Cochrane Database Syst Rev. 2014(1):10.1002/14651858.CD000009.pub3.
130. White HR, Bray BC, Fleming CB, Catalano RF. Transitions into and out of light and intermittent smoking during emerging adulthood. Nicotine & Tobacco Research. 2009;11(2):211-9.
131. Kang H-C, Shin K-K, Kim K-K, Youn B-B. The effects of the acupuncture treatment for smoking cessation in high school student smokers. Yonsei Med J. 2005;46(2):206-12.
132. Cai Y, Zhao C, Wong SU, Zhang L, Lim SK. Laser acupuncture for adolescent smokers—a randomized double-blind controlled trial. The American Journal of Chinese Medicine. 2000;28:443-9.
133. Audrain-McGovern J, Stevens S, Murray PJ, Kinsman S, Zuckoff A, Pletcher J, et al. The efficacy of motivational interviewing versus brief advice for adolescent smoking behavior

REFERENCES

change. Pediatrics. 2011;128(1):e101-e11.

134. Backinger CL, McDonald P, Ossip-Klein DJ, Colby SM, Maule CO, Fagan P, et al. Improving the future of youth smoking cessation. Am J Health Behav. 2003;27 Suppl 2:S170-84.
135. University Mental Health Research Institute (UMHRI). Nationwide Survey on Substance Use and other Addictive Behaviours in 16-year-old Students in Greece – ESPAD-Greece 2015 (unpublished data). Athens, Greece: University Mental Health Research Institute. 2015.
136. European Commission. Eurobarometer 72.3 Oral Health (2009). Brussels: TNS Opinion & Social. 2010.
137. Albert DA, Severson HH, Andrews JA. Tobacco use by adolescents: the role of the oral health professional in evidence-based cessation programs. Pediatr Dent. 2006;28(2):177-87.
138. Kentala J, Utriainen P, Pahkala K, Mattila K. Can brief intervention through community dental care have an effect on adolescent smoking? Prev Med. 1999;29(2):107-11.
139. Ackard DM, Neumark-Sztainer D. Health care information sources for adolescents: age and gender differences on use, concerns, and needs. J Adolesc Health. 2001;29(3):170-6.
140. Marcell AV, Halpern-Felsher BL. Adolescents' beliefs about preferred resources for help vary depending on the health issue. J Adolesc Health. 2007;41(1):61-8.
141. Heikkinen AM, Broms U, Pitkäniemi J, Koskenvuo M, Meurman J. Key factors in smoking cessation intervention among 15–16-year-olds. Behav Med. 2009;35(3):93-9.
142. Schauer GL, Agaku IT, King BA, Malarcher AM. Health care provider advice for adolescent tobacco use: results from the 2011 National Youth Tobacco Survey. Pediatrics. 2014:peds. 2014-0458.
143. Stein RJ, Haddock CK, O'Byrne KK, Hymowitz N, Schwab J. The pediatrician's role in reducing tobacco exposure in children. Pediatrics. 2000;106(5):e66-e.
144. American Academy of Pediatrics (Committee on Substance Abuse). Tobacco's toll: implications for the pediatrician. Pediatrics. 2001;107(4):794-8.
145. Lancaster T, Stead L. Individual behavioural counselling for smoking cessation. Cochrane Database Syst Rev. 2017(3):10.1002/14651858. CD001292.pub3.
146. Lando HA, Hennrikus D, Boyle R, Lazovich D, Stafne E, Rindal B. Promoting tobacco abstinence among older adolescents in dental clinics. Journal of Smoking Cessation. 2007;2(01):23-30.
147. Rice V, Stead L. Nursing interventions for smoking cessation. Cochrane Database Syst Rev. 2013(8):10.1002/14651858.CD001188.pub4.
148. Saari AJ, Kentala J, Mattila KJ. Long-term effectiveness of adolescent brief tobacco intervention: a follow-up study. BMC Res Notes. 2012;5:DOI: 10.1186/756-0500-5-101.

149. Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J, Lancaster T. Physician advice for smoking cessation. Cochrane Database Syst Rev. 2013(5):10.1002/14651858.CD000165.pub4.
150. Myers MG, Brown SA. A controlled study of a cigarette smoking cessation intervention for adolescents in substance abuse treatment. Psychology of Addictive Behaviors. 2005;19(2):230-3.
151. Brown RA, Ramsey SE, Strong DR, Myers MG, Kahler CW, Lejuez CW, et al. Effects of motivational interviewing on smoking cessation in adolescents with psychiatric disorders. Tob Control. 2003;12(SUPPL. 4):iv3-iv10.
152. Colby SM, Nargiso J, Tevyaw TO, Barnett NP, Metrik J, Lewander W, et al. Enhanced motivational interviewing versus brief advice for adolescent smoking cessation: Results from a randomized clinical trial. Addict Behav. 2012;37(7):817-23.
153. Horn K, Dino G, Hamilton C, Noerachmanto N. Efficacy of an emergency department-based motivational teenage smoking intervention. Preventing Chronic Disease. 2007;4(1):A08.
154. Hollis JF, Polen MR, Whitlock EP, Lichtenstein E, Mullooly JP, Velicer WF, et al. Teen reach: outcomes from a randomized, controlled trial of a tobacco reduction program for teens seen in primary medical care. Pediatrics. 2005;115(4):981-9.
155. Redding CA, Prochaska JO, Armstrong K, Rossi JS, Hoeppner BB, Sun X, et al. Randomized trial outcomes of a TTM-tailored condom use and smoking intervention in urban adolescent females. Health Educ Res. 2015;30(1):162-78.
156. UNICEF. Progress for Children: A report card on adolescents (No. 10): UNICEF2012 Contract No.: 978-92-806-4629-0.
157. Pbert L, Druker S, DiFranza JR, Gorak D, Reed G, Magner R, et al. Effectiveness of a school nurse-delivered smoking-cessation intervention for adolescents. Pediatrics. 2011;128(5):926-36.
158. Mermelstein R. Teen smoking cessation. Tob Control. 2003 Jun;12 Suppl 1:i25-34.
159. Aveyard P, Sherratt E, Almond J, Lawrence T, Lancashire R, Griffin C, et al. The change-in-stage and updated smoking status results from a cluster-randomized trial of smoking prevention and cessation using the transtheoretical model among British adolescents. Prev Med. 2001;33(4):313-24.
160. Guo JL, Liao JY, Chang LC, Wu HL, Huang CM. The effectiveness of an integrated multicomponent program for adolescent smoking cessation in Taiwan. Addict Behav. 2014;39(10):1491-9.
161. Sussman S, Arriaza B, Grigsby TJ. Alcohol, tobacco, and other drug misuse prevention and cessation programming for alternative high school youth: A review. J Sch Health.

REFERENCES

2014;84(11):748-58.

162. Burton D, Chakravorty B, Weeks K, Flay BR, Dent C, Stacy A, et al. Outcome of a tobacco use cessation randomized trial with high-school students. Subst Use Misuse. 2009;44(7):965-80.
163. Dalum P, Paludan-Müller G, Engholm G, Kok G. A cluster randomised controlled trial of an adolescent smoking cessation intervention: Short and long-term effects. Scandinavian Journal of Public Health. 2012;40(2):167-76.
164. Gonzálvez MT, Espada JP, Orgilés M, Soto D, Sussman S. One-year effects of Project EX in Spain: A classroom-based smoking prevention and cessation intervention program. PloS one. 2015;10(6):e0130595.
165. Espada JP, Gonzálvez MT, Orgilés M, Guillén-Riquelme A, Soto D, Sussman S. Pilot clinic study of Project EX for smoking cessation with Spanish adolescents. Addict Behav. 2015;45:226-31.
166. Zheng H, Sussman S, Chen X, Wang Y, Xia J, Gong J, et al. Project EX - a teen smoking cessation initial study in Wuhan, China. Addict Behav. 2004;29(9):1725-33.
167. Sussman S. International translation of Project EX: a teen tobacco use cessation program. Sucht. 2012;58(5):317-25.
168. Greenberg JS, Deputat Z. Smoking intervention: comparing three methods in a high school setting. J Sch Health. 1978;48(8):498-502.
169. Ha YS, Choi YH. Effectiveness of a motivational interviewing smoking cessation program on cessation change in adolescents. Journal of Korean Academy of Nursing [serial on the Internet]. 2012; (1): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/613/CN-00834613/frame.html.
170. Ha YS, Choi YH. Effectiveness of the self-determination theory based a motivational interviewing YOU-TURN program for smoking cessation among adolescents. Journal of Korean Academy of Nursing. 2015;45(3):347-56.
171. Kelly AB, Lapworth K. The HYP program—Targeted motivational interviewing for adolescent violations of school tobacco policy. Prev Med. 2006;43(6):466-71.
172. Peterson AV, Kealey KA, Mann SL, Marek PM, Ludman EJ, Liu J, et al. Group-randomized trial of a proactive, personalized telephone counseling intervention for adolescent smoking cessation. J Natl Cancer Inst. 2009;101(20):1378-92.
173. American Lung Association [ALA]. Not on Tobacco. Available at: http://www.lung.org/associations/states/colorado/tobacco/not-on-tobacco/. Accessed Dec 5, 2015.
174. Dino G, Horn K, Goldcamp J, Fernandes A, Kalsekar I, Massey C. A 2-year efficacy study of Not On Tobacco in Florida: An overview of program successes in changing teen smoking

behavior. Prev Med. 2001;33(6):600-5.
175. Horn K, Dino G, Branstetter SA, Zhang J, Noerachmanto N, Jarrett T, et al. Effects of physical activity on teen smoking cessation. Pediatrics. 2011;128(4):e801-e11.
176. Horn K, Dino G, Kalsekar I, Fernandes A. Appalachian teen smokers: Not On Tobacco 15 months later. Am J Public Health. 2004;94(2):181-4.
177. Horn K, Dino G, Kalsekar I, Mody R. The impact of Not-on-Tobacco on teen smoking cessation: End-of-program evaluation results, 1998 to 2003. Journal of Adolescent Research [serial on the Internet]. 2005; (6): Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/802/CN-00604802/frame.html.
178. Joffe A, McNeely C, Colantuoni E, An MW, Wang W, Scharfstein D. Evaluation of school-based smoking-cessation interventions for self-described adolescent smokers. Pediatrics. 2009;124(2):e187-e94.
179. Kohler CL, Schoenberger YMM, Beasley TM, Phillips MM. Effectiveness evaluation of the N-O-T smoking cessation program for adolescents. American Journal of Health Behavior. 2008;32(4):368-79.
180. Dino G, Horn K, Abdulkadri A, Kalsekar I, Branstetter S. Cost-effectiveness analysis of the not on tobacco program for adolescent smoking cessation. Prevention Science. 2008;9(1):38-46.
181. Horn K, Fernandes A, Dino G, Massey CJ, Kalsekar I. Adolescent nicotine dependence and smoking cessation outcomes. Addict Behav. 2003;28(4):769-76.
182. Chun J, Bae YJ, Min SK. Effectiveness of smoking cessation program for male adolescents in South Korea. Children and Youth Services Review. 2012;34(1):304-10.
183. Kong G, Larsen H, Cavallo DA, Becker D, Cousijn J, Salemink E, et al. Re-training automatic action tendencies to approach cigarettes among adolescent smokers: a pilot study. Am J Drug Alcohol Abuse. 2015;41(5):425-32.
184. Larsen H, Kong G, Becker D, Cavallo DA, Cousijn J, Salemink E, et al. Cognitive bias modification combined with cognitive behavioral therapy: a smoking cessation intervention for adolescents. Drug Alcohol Depend [serial on the Internet]. 2015: Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/582/CN-01077582/frame.html.
185. Haug S, Schaub MP, Venzin V, Meyer C, John U. Efficacy of a text message-based smoking cessation intervention for young people: a cluster randomized controlled trial. Journal of Medical Internet Research. 2013;15(8):doi: 10.2196/jmir.636.
186. Shi HJ, Jiang XX, Yu CY, Zhang Y. Use of mobile phone text messaging to deliver an individualized smoking behaviour intervention

REFERENCES

in Chinese adolescents. J Telemed Telecare. 2013;19(5):282-7.

187. Aveyard P, Bauld L. Incentives for promoting smoking cessation: what we still do not know. Cochrane Database Syst Rev. 2011(4):10.1002/14651858.ED000027.
188. Cahill K, Perera R. Competitions and incentives for smoking cessation. Cochrane Database Syst Rev. 2011;4.
189. Krishnan-Sarin S, Duhig AM, McKee SA, McMahon TJ, Liss T, McFetridge A, et al. Contingency management for smoking cessation in adolescent smokers. Experimental and Clinical Psychopharmacology. 2006;14(3):306-10.
190. Robinson LA, Vander Weg MW, Riedel BW, Klesges RC, McLain-Allen B. "Start to stop": results of a randomised controlled trial of a smoking cessation programme for teens. Tob Control [serial on the Internet]. 2003: Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/364/CN-00502364/frame.html.
191. Bühler A, Wegmann L, Schmidt A, Thrul J, Strunk M, Lang P. Rekrutierung, implementation und aufhörrate eines rauchstopp-kurses für jugendliche. Sucht. 2012;58(1):23-32.
192. Bailey SR, Hagen SA, Jeffery CJ, Harrison CT, Ammerman S, Bryson SW, et al. A randomized clinical trial of the efficacy of extended smoking cessation treatment for adolescent smokers. Nicotine and Tobacco Research. 2013;15(10):1655-62.
193. Norman CD, Maley O, Li X, Skinner HA. Using the internet to assist smoking prevention and cessation in schools: a randomized, controlled trial. Health Psychol. 2008;27(6):799.
194. Evers KE, Paiva AL, Johnson JL, Cummins CO, Prochaska JO, Prochaska JM, et al. Results of a transtheoretical model-based alcohol, tobacco and other drug intervention in middle schools. Addict Behav. 2012;37(9):1009-18.
195. Walters ST, Wright JA, Shegog R. A review of computer and Internet-based interventions for smoking behavior. Addict Behav. 2006;31(2):264-77.
196. Fritz DJ, Hardin SB, Gore Jr PA, Bram D. A computerized smoking cessation intervention for high school smokers. Pediatr Nurs. 2008;34(1):13-7.
197. Rodgers A, Corbett T, Bramley D, Riddell T, Wills M, Lin R-B, et al. Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile phone text messaging. Tob Control. 2005;14(4):255-61.
198. Patten CA, Croghan IT, Meis TM, Decker PA, Pingree S, Colligan RC, et al. Randomized clinical trial of an Internet-based versus brief office intervention for adolescent smoking cessation. Patient Educ Couns. 2006;64(1-3):249-58.
199. Chen HH, Yeh ML. Developing and evaluating a smoking cessation program combined with

an Internet-assisted instruction program for adolescents with smoking. Patient Educ Couns. 2006;61(3):411-8.
200. Lipkus IM, McBride CM, Pollak KI, Schwartz-Bloom RD, Tilson E, Bloom PN. A randomized trial comparing the effects of self-help materials and proactive telephone counseling on teen smoking cessation. Health Psychol. 2004;23(4):397-406.
201. Prokhorov AV, Kelder SH, Shegog R, Murray N, Peters R, Jr., Agurcia-Parker C, et al. Impact of a smoking prevention interactive experience (ASPIRE), an interactive, multimedia smoking prevention and cessation curriculum for culturally diverse high-school students. Nicotine Tob Res. 2008;10(9):1477-85.
202. Woodruff SI, Conway TL, Edwards CC, Elliott SP, Crittenden J. Evaluation of an Internet virtual world chat room for adolescent smoking cessation. Addict Behav. 2007;32(9):1769-86.
203. Flay BR. Understanding environmental, situational and intrapersonal risk and protective factors for youth tobacco use: the Theory of Triadic Influence. Nicotine & Tobacco Research. 1999;1(Suppl 1):S111-S4.
204. Prokhorov AV, Winickoff JP, Ahluwalia JS, Ossip-Klein D, Tanski S, Lando HA, et al. Youth tobacco use: a global perspective for child health care clinicians. Pediatrics. 2006;118(3):e890-e903.
205. Idrisov B, Sun P, Akhmadeeva L, Arpawong TE, Kukhareva P, Sussman S. Immediate and six-month effects of Project EX Russia: A smoking cessation intervention pilot program. Addict Behav. 2013;38(8):2402-8.
206. Patten CA, Fadahunsi O, Hanza MMK, Smith CA, Decker PA, Boyer R, et al. Tobacco cessation treatment for Alaska native adolescents: Group randomized pilot trial. Nicotine and Tobacco Research. 2014;16(6):836-45.
207. Lim MK, Kim HJ, Yun EH, Oh J-K, Park EY, Shin SH, et al. Role of quit supporters and other factors associated with smoking abstinence in adolescent smokers: A prospective study on Quitline users in the Republic of Korea. Addict Behav. 2012;37(3):342-5.
208. Patnode CD, O'Connor E, Whitlock EP, Perdue LA, Soh C, Hollis JF. Primary care–relevant interventions for tobacco use prevention and cessation in children and adolescents: A systematic evidence review for the US preventive services task force. Ann Intern Med. 2013;158(4):253-60.
209. US-Preventive-Services-Task-Force. Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: US Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2009;150(8):551. ■

3.
SMOKING CESSATION IN PATIENTSWITH DIABETES

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About this Guideline

This special chapter of the European Tobacco Treatment Guideline is intended to summarize evidence in terms of health risk associated with tobacco use among patients with diabetes as well as effective approaches to supporting cessation and preventing relapse.

Within the chapter clinical practice recommendations are presented for health care professionals working with diabetic patients. The GRADE evidence grading system has been used to rate the quality of evidence supporting each of the recommendations. The evidence grading scale reflects the type, quality and quantity of available evidence supporting the guideline recommendation. GRADE uses 4 evidence grading categories: 'high', 'moderate', 'low', 'very low' (see table below). The level of evidence grading appears in brackets at the end of each recommendation statement.

GRADE - Evidence Grading Categories:

CODE	QUALITY OF EVIDENCE	DEFINITION
A	High	– Further research is very unlikely to change our confidence in the estimate of effect. – Several high-quality studies with consistent results. – In special cases: one large, high-quality multi-center trial
B	Moderate	– Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. – One high-quality study. – Several studies with some limitations.
C	Low	– Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. – One or more studies with severe limitations.
D	Very Low	– Any estimate of effect is very uncertain. – Expert opinion. – No direct research evidence. – One or more studies with very severe limitations.

EXECUTIVE SUMMARY
SMOKING CESSATION IN PATIENTS WITH DIABETES

Health Effects of Smoking in diabetes patients

- Tobacco use is associated with a significant increase in risk of type 2 diabetes that is independent of educational level, physical activity, alcohol consumption, and diet. The risk of diabetes increases with greater tobacco consumption.
- Smoking among diabetic patients significantly amplifies the risk of coronary heart diseases, myocardial infarction, heart failure, stroke, peripheral arterial disease, cardiovascular mortality as well as total mortality. Tobacco use also increases microvascular complications in diabetic patients including an adverse effect on diabetic nephropathy.
- Exposure to passive smoking has been shown to increase the risk of developing metabolic syndrome, glucose intolerance and type 2 DM.

Health Benefits of Smoking Cessation

- While former smoking is associated with a higher risk of incident type 2 diabetes compared to never smoking, this risk decreases substantially as the time since quitting increases.
- Quitting smoking has been shown to substantially decrease risk of cardiovascular mortality as well as cardiovascular events among diabetic patients; however former smokers still have a higher risk of cardiovascular disease and mortality compared to never smokers.

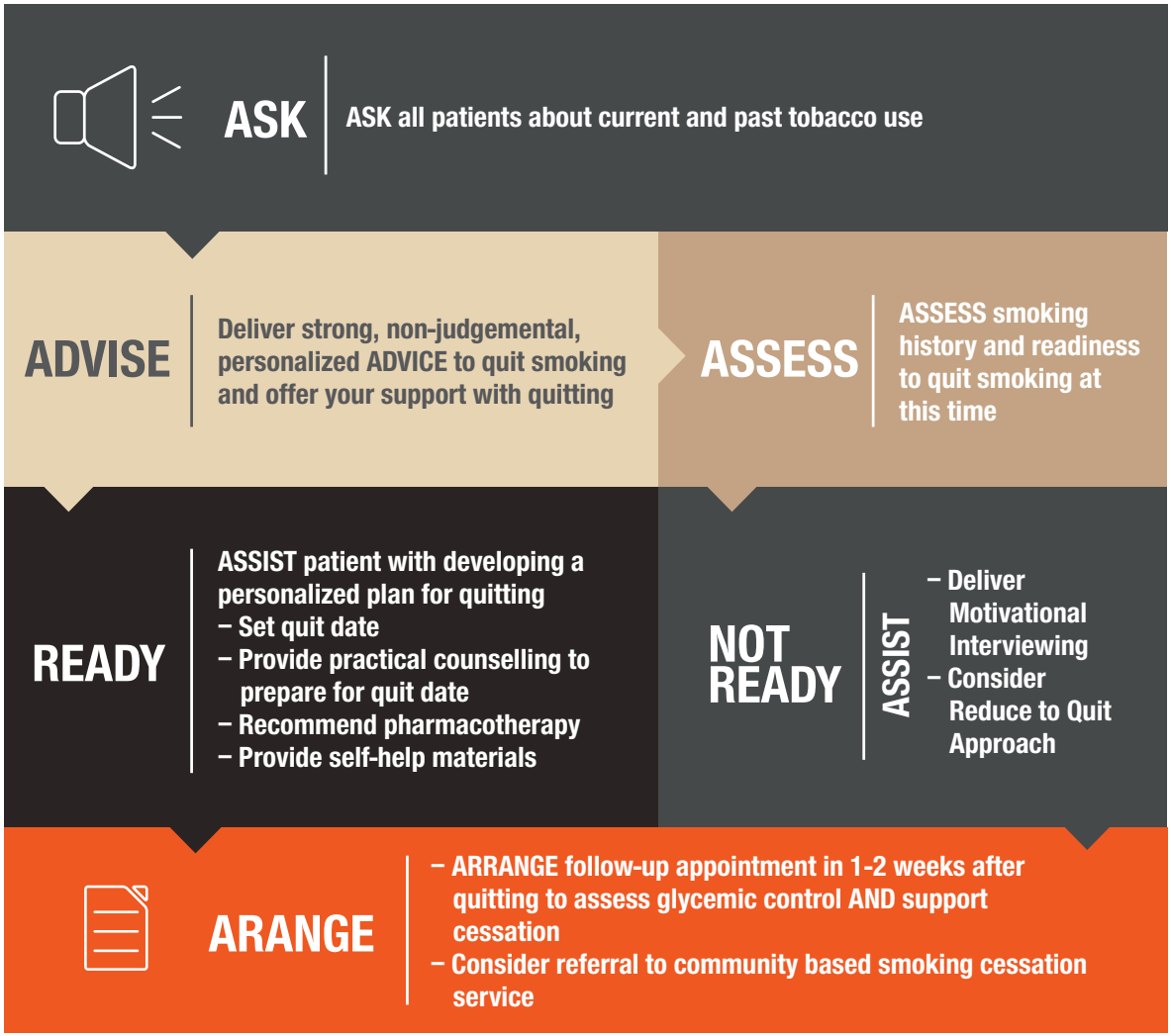
Important Considerations for diabetic patients

- It is vital to emphasize to young patients with diabetes how important it is not to start smoking, because, once they acquire the habit, they may find it difficult to give up.
- Despite the burden of tobacco use to the development and management of diabetes, the prevalence of smoking in diabetic patients remains very high in Europe.

- Tobacco users with diabetes are often inadequately informed about the benefits of quitting and/or available options to support cessation.
- In type 2 diabetics, smoking cessation is associated with deterioration in glycemic control that may last for 2-3 years and is unrelated to weight gain. Close monitoring of diabetic patients and adjustment of anti-diabetic medications to maintain effective glycemic control is needed following smoking cessation.
- Smoking Cessation Interventions in Diabetic Patients
- Evidence suggests that patients with diabetes do not easily adopt smoking cessation interventions and cessation success rates are often low.
- The prevention and cessation of tobacco use are important components of clinical diabetes care. All diabetic patients should have their current and past tobacco use documented. Patients reporting current tobacco use should be offered support with quitting as a priority. Smoking cessation interventions should include a combination of behavioural counselling and pharmacotherapy.
- Recommendations regarding efficacy of counselling based smoking cessation interventions among the population of patients with diabetes are limited by the small number of trials, relatively small sample size used in published trials, as well as, the heterogeneity in interventions tested to date. There are several examples of smoking cessation programs implemented in primary or/and secondary health care settings, which have shown beneficial effects for smoking cessation among diabetic patients.
- Evidence to guide best practice with regard to efficacy and safety of pharmacological treatment for smoking cessation is limited. As yet, no large-scale clinical trials reporting the efficacy and safety of nicotine replacement therapy bupropion or varenicline in patients with diabetes have been published. There is however no evidence to mitigate the use of these first-line quit smoking medications among diabetic patients. Due to the increased risk of seizure bupropion is not recommended for use among DM patients using hypo-glycaemic agents or insulin. Closer monitoring of blood sugar levels when first using quit smoking medications is recommended and adjustment of medication may be necessary.
- Key Recommendations for Health Professionals:
- Active tobacco use and second hand smoke exposure is associated with an increased risk of developing type 2 diabetes and should be regarded as major modifiable risk factors for type 2 diabetes (Level of Evidence A).
- Clinicians should clearly communicate to all patients who smoke the strong connection between smoking and second hand smoke exposure and the risk of developing type 2 diabetes, the risk being higher for those with a higher smoking intensity; and special attention should be given to those with other predisposing or risk factors for diabetes (Level of Evidence A).
- Clinicians should ensure assessment of tobacco use in diabetic patients and smoking cessation should be a clinical priority among diabetic patients who smoke (Level of Evidence A).

- Smoking cessation interventions should be initiated as an essential component of a smoking patient's diabetes treatment plan. Interventions should include a combination of behavioural counselling and pharmacotherapy (Level of Evidence A).
- The 5 'A's strategies are an effective method to address smoking cessation in clinical settings and are appropriate for use with diabetic patients (Level of evidence B).
- Smoking cessation interventions that are implemented in primary or/and secondary health care by different members of the health care team may have a beneficial effect on smoking cessation among diabetic patients, however the overall number of trials is limited (Level of Evidence B).
- Despite the limited number of trials that have tested the efficacy of first-line pharmacotherapies in diabetic patients, there is no evidence to mitigate the use of first-line quit smoking medications (NRT, bupropion and varenicline) among diabetic patients (Level of Evidence C).
- Due to the increased risk of seizure bupropion is not recommended for use among diabetic patients using hypo-glycaemia agents or insulin (Level of Evidence C).
- Due to the possible deterioration in glycaemic control in the first 2-3 years after quitting, clinicians should closely monitor glycaemia and adjust anti-diabetic medications to maintain effective glycaemic control following smoking cessation (Level of Evidence B).
- Closer monitoring of blood sugar levels when first using quit smoking medications is recommended and adjustment of medication may be necessary (Level of evidence B).

TOBACCO TREATMENT PROTOCOL – DIABETES PATIENTS



1.0
THE BASIS FOR SMOKING CESSATION AMONG DIABETIC PATIENTS

1.1 Smoking as a risk factor for diabetes mellitus

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[1]

Type I diabetes, which accounts for only 5–10% of those with diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. Type 2 diabetes accounts for 90–95% of those with diabetes and encompasses individuals who have insulin resistance and usually have relative insulin deficiency, without the autoimmune destruction of β-cells. Obesity and especially increased percentage of body fat distributed predominantly in the abdominal region increases the risk of type 2 diabetes.[1]

DM has become a global public health crisis, and the International Diabetes Federation estimated that 387 million adults were affected by diabetes mellitus in 2014 worldwide, a number which is predicted to continue to rise at an alarming rate, reaching 592 million by 2035.[2] Diabetes is a leading cause of cardiovascular mortality as well as of new cases of blind¬ness, kidney failure, and non-traumatic lower-limb ampu¬tation.[3] Beyond its unfortunate consequences for quality of life, the economic cost of diabetes is high. In 2010, the direct cost burden of people with diabetes was €43.2 billion in Germany, €20.2 billion in UK, €12.9 billion in France, €7.9 billion in Italy and €5.4 billion in Spain.[3]

It has been widely acknowledged that smoking is a leading risk factor for type 2 DM.[2,4] The European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct - a prospective case-cohort study within eight European countries, published in 2014 reported the hazard ratios (HR) of type 2 DM in men was 1.40 (95% CI 1.26-1.55) for former smokers and 1.43 (95% CI 1.27-1.61) for current smokers.[5] In women, associations were weaker, HR 1.18 (95% CI 1.07-1.30) and HR 1.13 (95% CI 1.03-1.25) for former and current smokers, respectively. For both men and woman the observed associations were independent of age, educational status, and lifestyle influences such as physical activity, alcohol consumption, and consumption of coffee and meat. There

was some evidence of effect modification by body mass index. The association tended to be slightly stronger in normal weight men compared with those with overall adiposity. Moreover, the study clearly shows that current smoking among men and women in the highest smoking intensity (cigarettes per day) had the highest hazard of type 2 DM compared with never smokers. Long-term quitters (more than 10 years since quitting) had a higher HR of type 2 DM than never smokers, but a lower HR than former smokers who quit more recently in both men and women.[5]

Similar findings were reported in a meta-analysis of 88 eligible prospective studies with 5,898,795 participants and 295,446 incident cases of type 2 DM published in 2015, which shows that the pooled relative risk (RR) of type 2 DM was 1.37 (95% CI 1.33–1.42) comparing current smoking with non-smoking (84 studies with n=5,853,952), 1.14 (95% CI 1.10–1.18) for former smokers compared with never smokers (47 studies with n=2,930,391). Again authors found the associations were higher for men than woman; RR for current smokers versus never smokers was 1.42 (95% CI 1.34-1.50) for men, and RR 1.33 for women (95% CI 1.26-1.41) respectively. The RR for former smokers versus never smokers was 1.16 (95% CI 1.10-1.22) for men and 1.12 (95% CI 1.05-1.20) for women. A dose-response relation for current smoking and DM risk was documented in this review as well. Compared with never smokers, the RRs were 1.21 (95% CI 1.10–1.33) for light smokers, 1.34 (95% CI 1.27–1.41) for moderate smokers, and 1.57 (95% CI 1.47–1.66) for heavy smokers. Based on the assumption that the association between smoking and diabetes risk is causal, it was estimated that 11.7% of cases of type 2 DM in men and 2.4% in women (i.e. approximately 27.8 million cases in total worldwide) were attributable to active smoking. Compared with never smokers, the pooled RR of developing diabetes based on data from ten studies with 1,086,608 participants was 1.54 (95% CI 1.36–1.74) for new quitters (<5 years), 1.18 (95% CI 1.07–1.29) for middle-term quitters (5–9 years), and 1.11 (95% CI 1.02–1.20) for long-term quitters (≥10 years).[6]

In 2014, the US Surgeon General's report, for the first time included a section of smoking and diabetes risk and summarized the biological basis of the causal relationship between tobacco use and smoking as follows:[4]

a. Many epidemiologic studies have shown that smoking is independently associated with an increased risk of central obesity, a well-established risk factor for insulin resistance and diabetes. Tobacco users tend to have higher concentrations of fasting plasma cortisol than non-smokers, which is associated with increased accumulation of visceral adipose tissue. Tobacco use also has independent effects on estrogens and androgens in women and decreases plasma testosterone in men, which may promote the accu¬mulation of abdominal fat;
b. Smoking increases inflammatory mark¬ers, oxidative stress and impairs endothelial function, which are all associated with the development of insulin resistance and irregularities in glucose metabolism;
c. Acute infusion of nicotine aggravates the insulin resistance status in people with type 2 DM;
d. Several animal model studies have revealed that exposure to nicotine, particularly in the prenatal or neonatal phases of life, can cause dysfunction of beta cells and increase beta-cell apoptosis, which is mediated via the mitochondrial and/or death receptor pathway.

1.2 Health Effects of Second Hand Smoke Exposure

There is good evidence regarding the causal relationship between second hand smoke (SHS) exposure and increased risk of developing metabolic syndrome, glucose intolerance and type 2 DM.

The Women's Health Study followed a large cohort (n=100,526) of women who did not have diabetes in 1982 for a period of 24-years.[7] The study documented an increased risk of diabetes among non-smokers who were occasionally (RR 1.10 [95% CI 0.94–1.23]) or regularly (RR 1.16 95% CI 1.00–1.35) exposed to SHS. Three recent meta-analyses have also reported on the association between SHS exposure and risk of Type 2 DM.[6,8,9] A meta-analyses involving 88 eligible prospective studies with 5,898,795 participants and 295,446 incident cases of type 2 DM published in 2015 identified seven studies (n=156,439) which focused on the risk of DM among never smokers who were exposed to passive smoking in comparison with never smokers without exposure to passive smoke. The results show that the RR of DM was 1.22 (95% CI 1.10–1.35) for comparing never smokers with and without exposure to passive smoke.[6]

A US-based prospective cohort study, involving fifteen years of follow-up of healthy adults aged 18-30 years examined the effect of biochemically verified SHS exposure and the risk of developing glucose intolerance (defined as glucose ≥ 100 mg/dl or taking anti-diabetic drugs).[10]

The study found among non-smoking individuals with SHS exposure the fifteen-year incidence of glucose intolerance was 17.2% with a HR of 1.35 (95% CI 1.06-1.71).

The association between second hand smoke exposure and metabolic disorders is not well known among health care professionals and the general public.

RECOMMENDATIONS:

- Active tobacco use and second hand smoke exposure is associated with an increased risk of developing type 2 diabetes and should be regarded as major modifiable risk factors for type 2 diabetes (Level of Evidence A).
- Clinicians should clearly communicate to patients the strong connection between smoking and second hand smoke exposure and the risk of developing type 2 DM, the risk being higher for those with a higher smoking intensity; and special attention should be given to those with other predisposing or risk factors for diabetes (Level of Evidence A).

1.3 Statistics about smoking prevalence and smoking patterns among diabetes patients

A meta-analysis published in 2015, which included 89 cohort studies concluded that the prevalence of smoking in diabetic patients remains high.[2] **Table 1** presents data on the prevalence of tobacco use among DM patients reported by several studies published between 1989 and 2015, based on the following geographical location: Europe, America, other countries.[2,11-50] The prevalence of smoking in diabetic patients varies greatly from country to country and seems to reflect the smoking habits of the general population.

TABLE 1: Prevalence of smoking among diabetic patients

STUDY	COUNTRY	AGE (YEARS)	SMOKING (%)
EUROPE			
Rosengren et al. 1989[11]	Sweden	51–59	40.5
Ostgren et al. 2002[12]	Sweden	>20	17
Nilsson et al. 2009[13]	Sweden	30–74	16.4
Morrish et al. 1991[14]	UK	35–55	65
Turner et al. 1998[15]	UK	25–65	69
Kothari et al. 2002[16]	UK	25–65	30
Laing et al. 2005[17]	UK	<40	36.17
Currie et al. 2010[18]	UK	≥50	63
Hadden et al. 1997[19]	Northern Ireland	40–69	36.8
Palmer et al. 2010[20]	Scotland	64.5 mean	50.8
Lehto et al. 1996[21]	Finland	45–64	16.5
Hu et al. 2005[22]	Finland	25–74	27.5
Lutgers et al. 2009[23]	Netherlands	66.4 mean	19.3
Muhlhauser et al. 2000[24]	Germany	27.5 mean	43
Rossing et al. 2001[25]	Germany	≥18	60
De Fine et al. 2010[26]	Germany	≥40	33
Muggeo et al. 2000[27]	Italy	56–74	22

STUDY	COUNTRY	AGE (YEARS)	SMOKING (%)
Faglia et al. 2002[28]	Italy	40–65	36.3
Bo et al. 2005[29]	Italy	≥35	22.3
Giorda et al. 2007[30]	Italy	40–97	52
Zoppini et al. 2009[31]	Italy	>35	
Mata-Cases et al. 2011[32]	Spain	58.9 for men 61.7 for female	40.8
Soedamah-Muthu et al. 2004[33]	16 European countries	15–60	49
Iversen et al. 2009[34]	Norway	≥20	17
Joergensen et al. 2010[35]	Denmark	<66	43.6
UNITED STATES			
Moy et al. 1990[36]	US	17–44	38
Ford et al. 1991[37]	US	25–74	32.3
Al-Delaimy et al. 2001[38]	US	30–55	20
Al-Delaimy et al. 2002[39]	US	30–55	20
Church et al. 2005[40]	US	21–99	65
Miller et al. 2009[41]	US	<18	51.5
Brown et al. 2010[42]	US	18–65	47
Nelson et al. 2010[43]	US	≥17	54
OTHER PARTS OF THE WORLD			
Florkowski et al. 2001[44]	New Zealand	30–82	15
Matsumoto et al. 2006[45]	Japan	59.6 mean	39
Davis et al. 2004[46]	Australia	64.1 mean	55.3
Norman et al. 2006[47]	Australia	64.1 mean	16.8
Ko et al. 2006[48]	Hongkong	16–95	28.2
Yang et al. 2007[49]	Hongkong	57 median	34
Yang et al. 2007[50]	Hongkong	>35	16.8

Daily cigarette consumption has been found in some cases to be higher among diabetic patients than among healthy people from the same population groups.[51] A study using US panel data from the National Longitudinal Study of Adolescent Health (Wave III 2001 to 2002) and (Wave IV 2007 to 2008), investigated the smoking behaviour among individuals who developed diabetes. Of 12,175 study participants, 2.6% reported having been diagnosed with diabetes in Wave IV. Early-onset diabetics (age at diagnosis <13 years) were more likely than non-diabetics to report frequent cigarette smoking (smoking on ≥ 20 days during the previous 30 days) in Wave IV (OR 3.34; 95% CI 1.27-8.79). On the other hand, late-onset diabetics (age at diagnosis ≥13 years) were more likely than non-diabetics to report heavy cigarette smoking (smoking ≥10 cigarettes per day during the previous 30 days) in Wave IV (OR 1.54; 95% CI 1.03-2.30).[52] Results from two German based studies, the Study of Health in Pomerania (SHIP) (n=4,283; 1997-2001) and the German National Health Interview and Examination Survey (GNHIES 98) (n=6,663; 1998) found that among current and former smokers the number of cigarettes smoked was higher among persons with than without type 2 DM.53 Among men this finding was seen in both the SHIP and GNHIES 98 studies, while for women this difference was only observed in the GNHIES 98 study.[53]

Finally, it should be kept in mind that tobacco use is often also a marker for many adverse and diabetes risk-influencing factors such as poor lifestyle, adverse social background factors, and more risk-taking behaviour.[54]

RECOMMENDATIONS:

- Future studies should investigate using longitudinal surveys the prevalence of smoking among diabetic patients from different countries, with a special focus for countries where this information is not available.

1.4 Effects of active smoking among diabetic patients

People with DM have an increased risk of developing a number of serious health problems, including macrovascular and microvascular complications. Several studies documented the adverse effect on smoking among diabetic patients.[2, 55-61]

1.4.1 Macrovascular complications

Tobacco use among DM patients is associated with increase morbidity and mortality. A meta-analysis which included 46 observational prospective studies with approximately 130,000 diabetic patients published in 2011 comparing smokers with non-smokers among DM patients reported a RR of 1.48 (95% CI 1.34–1.64) for total mortality (27 studies), RR 1.36 (95% CI 1.22–1.52) for cardiovascular mortality (9 studies), RR 1.54 (95% CI

1.31–1.82) for incidence of coronary heart diseases (13 studies), RR 1.44 (95% CI 1.28–1.61) for the incidence of stroke (9 studies) and RR 1.52 (95% CI 1.25–1.83) for the incidence of myocardial infarction (7 studies).[55] Furthermore, the excess risk was observed among former and current smokers with a greater risk in current smokers. Subgroup analysis showed that the increased risk was consistent despite differences in study characteristics with the RRs ranging from 1.31 to 1.94 for all-cause mortality, 1.37 to 2.28 for coronary heart diseases, 1.21 to 1.87 for stroke, 1.13 to 1.74 for cardiovascular mortality and 1.15 to 2.01 for myocardial infarction. Overall smoking was associated with a 36-54% excess risk of mortality or different vascular events among diabetic patients.[55]

A second meta-analysis published in 2015 which included 89 cohort studies found among diabetic patients the pooled adjusted RR associated with smoking was 1.55 (95% CI 1.46–1.64) for total mortality (48 studies, n=1,132,700), and RR 1.49 (95% CI 1.29–1.71) for cardiovascular mortality (13 studies, n=37,550).[2] The pooled RR was 1.44 (95% CI 1.34–1.54) for total cardiovascular disease (CVD), RR 1.51 (95% CI 1.41–1.62; 16 studies) for coronary heart disease (21 studies), RR 1.54 (95% CI 1.41–1.69) for stroke (15 studies), RR 2.15 (95% CI 1.62–2.85) for peripheral arterial disease (3 studies), and RR 1.43 (95% CI 1.19–1.72) for heart failure (4 studies). In comparison with never smokers, former smokers were at a moderately elevated risk of total mortality (RR 1.19; 95% CI 1.11– 1.28), cardiovascular mortality (RR 1.15; 95% CI 1.00–1.32), CVD (RR 1.09; 95% CI 1.05–1.13), and coronary heart disease (1.14; 1.00–1.30), but not for stroke (RR 1.04; 95% CI 0.87–1.23). Active smoking was associated with an approximate 50% increased risk of total mortality and CVD among diabetic patients.[2]

1.4.2 Microvascular complications

The effects of tobacco use on microvascular diabetes complications vary across reports. Generally, several studies have shown that tobacco use has an adverse effect on diabetic nephropathy. Studies have demonstrated that smoking promotes diabetic microalbuminuria and exacerbates diabetic nephropathy. In a 13-year follow-up study by Biesenbach et al., the progression of nephropathy was clearly increased in smokers.[58] The authors found that smoking was a risk factor for dia¬betic kidney disease, independent of age, sex, and duration of diabetes and HbA1c levels.[58] In prospective studies by Chuahirun and Wesson [59] and Chuahirun et al.[60] the adverse effects on diabetic nephropathy in type 2 patients were confirmed, even among optimal hypertensive patients.

The influence of smoking independent of glucose control on retinopathy is less clear.[56,57] Some studies have reported no association with smoking and retinopathy in type 2 diabetes.[61,62] It was reported that retinopathy has been associated with glycemic control and not smoking state.[61] The United Kingdom Prospective Diabetic (UKPD) study which sought to examine risk factors related to the incidence and progression of diabetic retinopathy, followed patients over 6 years from diagnosis. The development of retinopathy was associated with

glycemia and higher blood pressure, but not smoking.[63] A European study assessing the relationship between smoking and microvascular complications in patients with type 1 DM found current smokers had poorer glycemic control and a higher prevalence of microalbuminuria and retinopathy than never-smokers, the odds of experiencing albuminuria and retinopathy in current smokers in comparison with never smokers being 1.60 and 1.62, respectively (after adjusting for age, duration, SBP, education, center, and HbA1c).[64] The authors suggested that smoking is associated with poorer glycemic control, which may also lead to microvascular complications, the prevalence of retinopathy and microalbuminuria in current smokers being not only due to poor glycemic control.[60] A review of cigarette smoking and diabetes also acknowledged an increased risk and accelerated progression of retinopathy in patients with type 1 diabetes.[65] A review on smoking and macular degeneration among general population showed, independent of DM, that active smoking is an important risk factor for macular degeneration and consecutive blindness.[66,67]

A systematic review and meta-analyses published in 2015 investigated the relationship between smoking and diabetic peripheral neuropathy (DPN) in persons with type 1 or type 2 DM.[68] Thirty-eight studies (10 prospective cohort and 28 cross-sectional) were included. The prospective cohort studies included 5,558 participants. The analysis of cross-sectional studies (n=27,594) reported a pooled OR of DPN associated with smoking was 1.42 (95 % CI 1.21–1.65; I2=65%;).[68] Smoking may affect diabetic neuropathy differently according to the type of DM; while not being a risk factor for people with type 2 DM, several studies underline that the situation could be different for those with type I DM.[58,59,60] More studies are needed to evaluate the association between smoking and peripheral neuropathy.

1.4.3 Smoking and the risk of hypoglycaemia

The complications induced by smoking in patients with DM may also include an increased risk of hypoglycaemia, at least in patients with type 1 DM. In a population of 537 patients with long-term type 1 DM, current smokers were found to have increased odds of severe hypoglycaemia compared with never-smokers (OR 2.4; 95% CI 1.30–4.40).[69]

1.5 Specific health concerns after quitting smoking

1.5.1 Weight gain

Smoking cessation reduces the risk of CVD, but there are concerns that weight gain that follows quitting smoking may weaken the CVD benefit of quitting. The results of the prospective community-based cohort study using data from the Framingham Offspring Study collected from 1984 to 2011 found that weight gain fol-

lowing smoking cessation does not attenuate the benefits of smoking cessation among people with and without diabetes.[70] After a mean follow-up of 25 years (SD 9.6), 631 CVD events occurred among 3,251 participants. Median 4-year weight gain was greater for recent quitters without diabetes (2.7 kg, Interquartile range [IQR] 0.5-6.4) and with diabetes (3.6 kg, IQR 1.4-8.2) than for long-term quitters (0.9 kg, IQR 1.4-3.2 and 0.0 kg, IQR 3.2-3.2, respectively, p<0.001). Among smokers without diabetes, age and sex-adjusted incidence rate of CVD was 5.9/100 person-exams (95% CI 4.9-7.1), 3.2/100 person-exams (95% CI 2.1-4.5) in recent quitters without diabetes, 3.1/100 person-exams (95% CI 2.6-3.7) in long-term quitters, and 2.4/100 person-exams (95% CI 2.0-3.0) in non-smokers. After adjustment for CVD risk factors, compared with smokers, recent quitters had a HR for CVD of 0.47 (95% CI 0.23-0.94) and long-term quitters had an HR of 0.46 (95% CI 0.34-0.63); these associations had only a minimal change after further adjustment for weight change. Among people with diabetes, there were similar point estimates that did not reach statistical significance.[70]

1.5.2 Glycaemic control

There is an increasing concern regarding glycaemic control after quitting smoking.[56,57] A prospective study from the UK, which included 10,692 adult smokers with type 2 DM investigated the effect of quitting smoking on HbA1c.[71] A total of 3,131 (29%) of participants quit smoking and remained abstinent for at least 1 year. After adjustment for potential confounders, HbA1c increased by 0.21% (95% CI 0.17–0.25; p<0.001) or 2.34 mmol/L (95% CI 1·91–2·77) within the first year after quitting. HbA1c decreased as abstinence continued for a period of up to 3 years. The observed increase in HbA1c was not mediated by weight change.[71] These findings emphasize the need for proactive review of glycaemic control and prompt adjustment of medication when patients with type 2 diabetes quit smoking. [56]

RECOMMENDATIONS:

- Due to the possible deterioration in glycaemic control in the first 2-3 years after quitting, clinicians should closely monitor glycaemia and adjust anti-diabetic medications to maintain effective glycaemic control following smoking cessation (Level of Evidence B).

1.6 Barriers for quitting smoking and risk factors for relapse among diabetic patients

We review here barriers for quitting smoking and risk factors for relapse among DM patients based on individual characteristics of patients and characteristics of the available medical care.

1.6.1 Individual characteristics

Evidence suggests that patients with diabetes do not easily adopt smoking cessation interventions and cessation success rates are often low. Studies have found advice to quit smoking, which has been shown to be a successful form of intervention among other disease groups, has lower impact on diabetic patients.[56] In addition high rates of drop out from smoking cessation program has been reported by some groups. In a prospective study of 70 diabetic smokers, only 50% agreed to participate in an anti-smoking programme, and the drop out rate was high irrespective of whether the content of the program was general or specific for diabetes.[72] The enrolment rate was highest two months after the diagnosis of diabetes and the drop out rate was highest in patients recruited immediately following diagnosis.[72]

There are several potential barriers for quitting smoking. First, people with diabetes frequently explain their inability to stop smoking by saying they are already too restricted by the diabetic treatment regimen, particularly the diet, and that they develop a 'craving' for cigarettes when deprived of nicotine.[51] The marked and almost unbearable unpleasantness experienced after abstinence from nicotine often induces a desire to eat sweet carbohydrates, which appear to modulate and improve mood and lead to weight gain. This observation may explain why patients with diabetes, who are forbidden to consume large amounts of sugary foods, are afraid of quitting smoking and to some extant less capable to cope with nicotine withdrawal.[51] Second, diabetic patients are also more likely to suffer from depression or anxiety, conditions known to hinder efforts to stop smoking.[73,73] Third, several misconceptions about the association between diabetes and smoking might be present, including the perceived hazards of quitting. Fourth, fear regarding weight gain after cessation may make quitting challenging.[51,74]

Adolescents with diabetes are of particular concern. In a qualitative study conducted among Swedish adolescents, Regber and Kelly evaluated why adolescents with diabetes choose to smoke, despite presumed awareness of health risks.[75] Reasons for their cigarette use behaviours included pure experimentation, identity development, the need to conform to group norms, and denial of health risks. The same study also found that few adolescents reported taking advice from health professionals regarding cigarette smoking. Studies have suggested that young people with chronic conditions are more vulnerable and subjected to more pressures to conform to group norms.[75,76,77] Young people with chronic conditions may feel a greater need to be accepted by their healthy counterparts, with engagement in risk-taking behaviours including cigarette smoking serving to substantiate their fitness and reinforce their self-esteem.[77]

1.6.2 Medical care

Patients with DM see health care professionals from primary and/or secondary health care centres more often than members of the general population, which offers the opportunity to assess smoking behaviour, give advice to stop smoking and offer smoking cessation counselling or encourage referral to resources where they can receive the appropriate assistance with quitting. Nevertheless, the results of studies from different countries show a diverse situation, with studies reporting low involvement of health care professional in assessing and advising smoking cessation among DM patients, while other studies observed a different situation.[51,56,57,78,79,80] The barriers to delivering advice and counselling for smoking cessation for both patients with diabetes as well as persons at risk for developing diabetes include: [51,74,80,81]

- Lack of time, motivation or training of health care professionals for the delivery of smoking cessation interventions;
- A disease management approach which focuses more on glycaemia control, lowering cholesterol levels and blood pressure versus cessation;
- Inappropriate funding and limited access to smoking cessation services in some countries.

RECOMMENDATIONS:

- Behavioural counselling for smoking diabetic patients which counter misconceptions about quitting smoking and help them to develop new strategies to deal with life stressors and weight control are essential for smoking cessation components in a comprehensive smoking cessation intervention (Level of evidence B).
- Future studies should continue to investigate the barriers for smoking cessation among DM patients from both developed and developing countries and to develop appropriate strategies for counteracting them.

2.0
INTERVENTIONS FOR SMOKING CESSATION IN DIABETIC PATIENTS

2.1 Integrating smoking cessation treatment into diabetes management

Smoking cessation should be a priority for diabetic patients who smoke. Tobacco treatment interventions should be initiated as an essential component of a patient's DM treatment plan.[79] The American Diabetic Association makes the following recommendations for encouraging smoking cessation among diabetic patients:[82,83]

Assessment of smoking status and history

- Systematic documentation of a history of tobacco use must be obtained from all adolescent and adult individuals with diabetes.

Counselling on smoking prevention and cessation

All health care providers should advise individuals with diabetes not to initiate smoking. This advice should be consistently repeated to prevent smoking and other tobacco use among children and adolescents with diabetes under age 21 years.

- Among smokers, cessation counselling must be completed as a routine component of diabetes care.
- Every smoker should be urged to quit in a clear, strong, and personalized manner that describes the added risks of smoking and diabetes.
- Every diabetic smoker should be asked if he or she is willing to quit at this time.
  i. If not, initiate brief and motivational discussion regarding need to stop using tobacco, risks of continued use, and encouragement to quit as well as support when ready.
  ii. If yes, assess preference for and initiate either minimal, brief, or intensive cessation counseling and offer pharmacological supplements as appropriate.

Effective systems for delivery of smoking cessation

- Training of all diabetes health care providers in the Public Health Service guidelines regarding smoking should be implemented.
- Follow-up procedures designed to assess and promote quitting status must be arranged for all diabetic smokers.

2.2 The 5 'A's Model

The 5 'A's (ask, advise, assess, assist, arrange) model for addressing tobacco use is recommended in all clinical settings.[84] The 5 'A's has been demonstrated as an effective method to address smoking cessation in the general population, but its use and effectiveness among diabetic patients is not as well studied.[84] The model recommends all health care professional involved in the care of diabetes patients should document the smoking status of all diabetic patients (Ask), advise all tobacco users to quit (Advise), and assess the willingness of all tobacco users to make a quit attempt at this time (Assess), and offer evidence-based treatments to support cessation (Assist) which includes arranging follow-up or specialized support with quitting (Arrange).[84-86] A summary of these strategies for use in the management of diabetes are displayed in **Table 2** and clinical protocol in **Figure 1**.

This 5 'A's model was used by a study performed among 224 adult diabetes patients aged 18 years or older who smoked in the last month, from two diabetes clinics in South India.[87,88] The objective of the study was to document the effectiveness of diabetic specific smoking cessation counselling by a non-doctor health professional in addition to a cessation advice delivered by physicians. The study included 2 intervention groups and a control group comparator. Patients from both groups received smoking cessation advice at each visit from the physician for the next six months. Intervention group patients received three diabetic specific tobacco counselling sessions (at first contact, 1 and 3 months) lasting about 30 minutes each which used the 5 'A's and 5 'R's (Relevance, Risks, Rewards, Roadblocks and Repetition). In the first session, after going over the educational material, developed for smoking cessation, with the patient (to establish relevance and support the doctor's advice) the counsellor assessed each patient's readiness to quit. If ready to quit, the counsellor assisted him by discussing practical quit tips, how to get through an initial period of withdrawal, and how to deal with common withdrawal symptoms, emphasizing that these only lasted for a few days. If not ready to quit, the counsellor briefly identified roadblocks and challenges to quitting, and encouraged the patient to think about quitting after reconsidering the risks of smoking for developing diabetes complications and the benefits of quitting as a means of preventing complications as a prime motivator. The results show that at 6 months follow-up the odds of quitting (abstinence of smoking for at least 7 days) was 8.4 [95% CI 4.1-17.1] for the intervention group compared to control group. Even among highly dependent smokers the odds of quitting were similar. The odds of harm reduction (reduction of smoking more than 50% of baseline use) were 1.9 (CI: 0.8-4.1) for intervention group compared to control group.[88] Salivary cotinine tests after 1-year follow-up confirmed self-reported cessation in 86%. Odds of quitting in intervention group, adjusted for age, education, occupation, presence of any other chron-

ic disease, duration of diabetes, and number of cigarettes/bidis smoked per day at baseline, were significantly higher compared with control group (AOR 3.35; 95% CI 1.82–6.18). Similarly, the odds of harm reduction in the intervention group were higher compared with the control group (AOR 2.21; 95% CI 1.24–3.93).[88]

TABLE 2: The use of 5A's for smoking prevention and cessation diabetes patients

FIVE A'S STEPS	APPLICATIONS AMONG DM PATIENTS
Ask all patients about smoking and other tobacco use along with other behaviours that influence Type 1 DM management	– Ask about smoking along with other health behaviours, including glucose monitoring, diet, and physical activity – Include smoking as a vital sign to be assessed for all patients – Incorporate cues and reminders for providers to ask about smoking
Advise all patients to avoid smoking and other tobacco use	– Emphasize the costs of smoking to DM management/outcomes – Tailor advice to patient's smoking status, emphasizing importance of continuing to avoid smoking for non-smokers and quitting smoking for smokers – Equip providers with knowledge and skills to implement proven intervention methods through in-service trainings, continuing education, and other strategies
Assess susceptibility to smoking among non-smokers and readiness to quit smoking among current smokers	– Identify risk factors that influence smoking susceptibility and readiness to quit, including risk perceptions, exposure to family/friends who smoke, and diabetes regimen non-adherence – Use strategies such as the 5 R's to enhance motivation to avoid or stop smoking – Emphasize the benefits of avoiding smoking for diabetes care and the risks for adverse health outcomes caused by smoking.

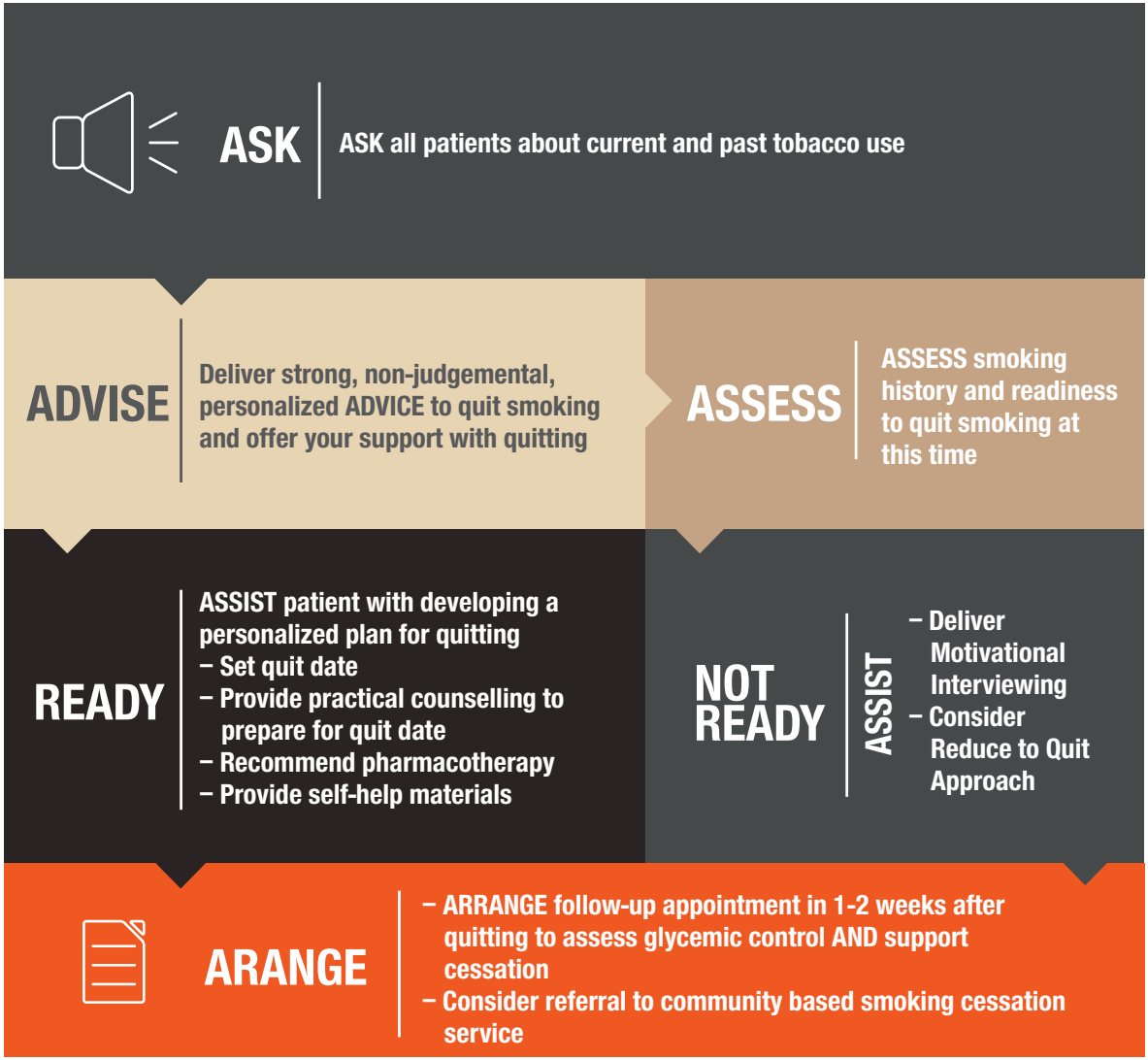
FIVE A'S STEPS	APPLICATIONS AMONG DM PATIENTS
Assist all patients with smoking avoidance/ cessation as part of routine care	– Use simple tools, such as quick guides and checklists, which can be adapted to include diabetes-specific content – Integrate motivational enhancement strategies, such as experiential learning, role playing, and patient education – Educate patients and families about the importance of a smoke-free environment and provide referral and treatment for cessation among smokers
Arrange for follow-up to continually monitor smoking behaviours among all patients as part of routine diabetes care	– Routinely evaluate smoking behaviours as part of regular type 1 diabetes management appointments – Provide patients and their families with education and counselling resources available adjunct to standard care, such as counselling interventions and materials, available through electronic media – Consider additional treatment options for cessation among patients who continue to smoke

Source: Adapted from Mays et al (2012) [86]

RECOMMENDATIONS:

- Clinicians should ensure assessment of tobacco use in diabetic patients and smoking cessation should be a clinical priority among diabetic patients who smoke (Level of Evidence A).
- Smoking cessation interventions should be initiated as an essential component of a smoking patient's diabetes treatment plan. Interventions should include a combination of behavioural counselling and pharmacotherapy (Level of Evidence A).
- The 5 'A's strategies are an effective method to address smoking cessation in clinical settings and are appropriate for use with diabetic patients (Level of evidence B).

FIGURE 1: Tobacco Treatment Protocol for Diabetes Patients



2.3 Non-pharmacological interventions

There is limited data to report on the efficacy of smoking cessation interventions among DM patients nor the best strategies to maximize success with quitting.[56,57,89] Several controlled trials targeting patients with diabetes have been published recently. Results were mixed, with positive effects found in studies with larger sample sizes.[56,83,89]

A systematic review and meta-analysis of randomised trials of smoking cessation interventions published in 2014 evaluated the effects of more intensive smoking cessation interventions compared to less intensive interventions (control group or those with optional medication) on smoking cessation in people with type 1 or type 2 DM published up to 2013.[89] The review did not include trials in which smoking cessation was a part of a more extensive complex intervention and in which only a proportion of patients had diabetes and smoked at baseline. Eight eligible trials (n=872) were identified which reported on smoking cessation outcomes at 6-months of follow-up however only four were eligible for inclusion in the meta-analysis. Three trials were carried out in Europe, two in Asia, two in Australia and one in North America. Five trials assessed either non-pharmacological interventions to support smoking cessation or referral to a smoking cessation clinic. Interventions reported in three other trials included optional nicotine replacement therapy (NRT) or bupropion. The meta-analysis reported a non-significant increase in self-reported smoking cessation outcomes for more intensive interventions (RR 1.85; 95% CI 0.81 to 4.22) compared with patients allocated to the less intensive intervention.[89] A similar pattern was found when biochemically verified smoking abstinence was assessed by intervention intensity (RR 1.32; 95% CI 0.23 to 7.43). However significant heterogeneity was reported (I2= 76%) with equal numbers of studies reporting positive and negative effect estimates. No specific conclusions regarding intensity of intervention can be drawn from available literature.[89]

The limited number of studies, heterogeneity in intervention tested and comparator groups limits the ability to draw conclusions regarding the efficacy and characteristics of smoking cessation interventions among DM patients used alone or in combination with medication.

RECOMMENDATIONS:

- Recommendations regarding the efficacy of smoking cessation interventions for diabetic patients are limited by the small number of trials published to date and a relatively small number of participants in published trials as well as the heterogeneity of interventions tested.

2.3.1 Types of interventions

We review here evidence for the different types of non-pharmacological interventions tested among DM patients including: cognitive behavioural interventions, stage-based interventions and motivational interviewing. Table 3 presents examples of smoking cessation interventions implemented in different countries in primary or secondary health care settings or both of them.

TABLE 3: Smoking cessation interventions for DM patients

STUDY (YEAR)	COUNTRY	SETTING	DESCRIPTION OF THE INTERVENTION	TYPE OF NON-PHARMACOLOGICAL INTERVENTIONS	PHARMACOLOGICAL TREATMENT
Thankappan et al (2014,2015) [87,88]	India	Diabetes clinics	Physician advice followed by nurses who delivered individual counselling	5A's Cognitive-behavioural therapies	No
Perez-Tortosa (2015) [90]	Spain	Primary care settings	Mixed teams of physician and nurses delivered several sessions of individual counselling	Stages of change Motivational interviewing	Yes, but not specified
Ng et al. (2010) [91]	Indonesia	Diabetes clinics	Medical doctors delivered advice and visual materials with referral to cessation clinic	Not specified	No
Davies et al. (2008) [92]	UK	Primary care settings	Health educators delivered several sessions of group education	Behavioural therapy	No
Persson et al. (2006) [93]	Sweden	Primary care settings	Nurses delivered several sessions of group and telephone counselling	Motivational interviewing	Optional, NRT or bupropion
Hokanson et al. (2006) [94]	USA	Diabetes center	Nurses delivered individual and telephone counselling	Motivational interviewing	Optional, NRT or bupropion
Canga et al. (2000) [95]	Spain	Primary care settings and hospitals	Nurses delivered both individual counselling as well as telephone follow up	Stages of change Cognitive-behavioural therapies	Optional, NRT
Sawicki et al. (1993) [96]	Germany	Outpatient university clinic	Therapists delivered 10 weekly individual counselling	Behavioural therapy	Optional, NRT

	CONTROL GROUP	PRIMARY OUTCOME	EFFECTS AT FOLLOW UP IN THE INTERVENTION GROUP IN COMPARISON WITH THE CONTROL GROUP
	Doctor's advice and educational materials	Self-reported measures 7-day abstinence	Stronger effect for smoking cessation at 6 months and one year in comparison with the control group; adjusted OR 8.4 (95% CI 4.1 to 17.1), respectively 3.35 (95% CI 1.82–6.18)
	Usual care	Continued abstinence defined as at least 6 months without smoking and a carbon monoxide (CO) breath level of <6 ppm	Stronger effect for smoking cessation at 1 year in comparison with the control group ($p<0.01$ at x2 test for difference in abstinence rate)
	Doctor's advice and visual materials	Self-reported measures 7-day abstinence	In both groups there were observed positive results for smoking cessation and no statistically significant differences were found between the groups
	Usual care	Self-reported measures 7-day abstinence	Stronger effect for smoking cessation at 12 months in comparison with the control group; The odds of not smoking were 3.56 (95% CI 1.11 to 11.45), P=0.033 higher in the intervention group at 12 months.
	A letter with general advice for smoking cessation	Self-reported abstinence	Stronger effect for smoking cessation at 6 months in comparison with the control group; ($p<0.01$ at x2 test for difference in abstinence rate)
	Standard care including referral to cessation program	Biochemically verified smoking cessation	Stronger effect for smoking cessation at 3 months follow up, but not at 6 months in comparison with the control group
	Usual care - advise to stop smoking	Biochemically verified smoking verified smoking	Stronger effect for smoking cessation at 6 months in comparison with the control group; incidence ratio 7.5 (95% CI 2.3 to 24.4)
	A single unstructured session by a physician with optional NRT	Biochemically verified smoking cessation	Similar effect on smoking cessation at 6 months in comparison with the control group

Cognitive behavioural interventions

Cognitive behavioural interventions alone or in combination with medication proved to be effective tools for smoking cessation among general population.[97] There are also some examples of studies, which used this approach for smoking cessation among diabetic patients.

In a diabetes outpatient university clinic from Germany, behaviour therapy for smoking cessation was compared with a single unstructured anti-smoking advice session given by a physician.[96] The number of self-reported cigarettes per day was successfully reduced during behaviour therapy treatment. There was no significant difference between the number of successful quitters in each group, indicating that in terms of abstinence in the long-term, the behavioural therapy was no more successful than more general GP advice, in this instance.[96]

A structured group education program known as DESMOND was conducted in general practices and primary care sites in the UK for newly diagnosed patients with type 2 diabetes.[92] Patients were randomized to either the group education intervention, or usual care, and the intervention took place within 12 weeks of diagnosis. The intervention incorporated advice on medication and psychological theories of learning aimed at reducing personal risk factors through lifestyle choices. At 12 months, there was a significant reduction in the number of smokers in the intervention group compared with the control group at 8 and 12 months ($p=0.033$) and these patients also reported being more physically active and less depressed. The outcomes of this study indicate that targeting and educating patients soon after diagnosis can successfully improve lifestyle choices, including smoking status, and have a positive impact on physical and psychological wellbeing.[92]

Stage-based interventions

The Transtheoretical Model of Change (TTM) identifies 6 stages of change: pre-contemplation, contemplation, preparation, action, maintenance, and relapse. Pre-contemplation is the period in which smokers were not considering quitting smoking (at least not within the next 6 months). Contemplation is the period in which smokers are seriously thinking about quitting smoking within the next 6 months. The preparation stage described the period when smokers are seriously thinking about quitting smoking within the next month and had also tried to quit smoking during the past year. Action is the period ranging from 0 to 6 months after smokers had made the overt change of stopping smoking. Maintenance is the period beginning 6 months after action had started. Relapse occurs when smokers who have tried to quit return to active smoking.[84]

One longitudinal descriptive study from the US evaluated the use of stages of change for cessation of smoking among diabetic patients.[98] For pre-contemplation subjects, a brief session was carried out where information regarding the risks of smoking in conjunction with DM was given. Patients at the contemplation stage of smoking cessation were offered the chance to participate in a cessation program. Seven hundred thirty-three subjects with DM were evaluated, including 156 smokers (21.3%): 66.0% in the pre-contemplation stage, 16.0% in the contemplation stage, 7.7% in the preparation stage, 7.7% in the action stage, and 2.6% in the maintenance

stage. By the 6-month follow-up, 41.6% subjects had quit smoking, of whom 30.8% had subsequently relapsed. This approach resulted in an increased change of smoking cessation stages in subjects with DM as well as a higher overall percentage in abstinence.[98]

Another study from Spain assessed the effectiveness of an intensive smoking cessation intervention based on the TTM in diabetic smokers attending primary care.[90] A cluster randomized controlled clinical trial was designed in which the unit of randomization (intervention vs. usual care) was the primary care team. An intensive, individualized intervention using motivational interviewing and therapies and medications adapted to the patient's stage of change was delivered by primary care teams including physicians and nurses. The number of intervention visits varied according to the stage of the patient (five for pre-contemplation, seven for contemplation and eight for preparation/action). Patients could move forward and backward in their stage over the course of the study, so that intervention visits were adapted to these changes. The duration of the study was 1 year and included 722 people with diabetes who were smokers (345 in the intervention group and 377 in the control group). After 1 year, continued abstinence was recorded in 26.1% patients in the intervention group and in 17.8% controls (p=0.007). In patients with smoking abstinence, there was a higher percentage in the pre-contemplation and contemplation stages at baseline in the intervention group than in controls (21.2% vs. 13.7%, p=0.024). When the pre-contemplation stage was taken as reference, preparation/action stage at baseline showed a protective effect, decreasing 3.41 times odds of continuing smoking (OR 0.29 95% CI 0.179–0.479). The authors conclude that an intensive intervention adapted to the individual stage of change delivered in primary care was feasible and effective, with a smoking cessation rate of 26.1% after 1 year.[90]

Canga and colleagues implemented a smoking cessation intervention for diabetic patients in Spain where the intervention was tailored to each patient depending on their stage of change and whether the patient agreed to set a cessation date.[95] This randomized controlled clinical trial involved 280 diabetic smokers who were randomized either into control (n=133) or intervention (n=147) groups at 12 primary care centres and 2 hospitals. The intervention protocol consisted of 3 parts: 1) an initial face-to-face interview, 2) optional nicotine replacement therapy (NRT), and 3) a follow-up support program. The control group received the usual care for diabetic smokers. Subjects assigned to the intervention group had a face-to-face interview with a nurse who was a member of the research team. This initial visit lasted 40 min, during which the nurse clearly advised each smoker to stop smoking. The nurse personalized the message by adapting it into the patient's clinical condition, smoking history, and personal interests. The nurse provided a list of the different reasons to stop smoking, highlighted the advantages of quitting rather than the risks of continued smoking, and tried to transmit a positive message by stressing the particular benefits of quitting for diabetic patients (e.g., reducing the baseline higher risk of stroke, coronary heart disease, peripheral artery disease, retinopathy, and nephropathy and improving insulin action). A cessation date was negotiated with those patients who were willing to stop. Self-help materials with quitting cues were also provided. The follow-up program was scheduled according to the negotiated ces-

sation date. It consisted of 5 contacts: 1) a telephone call the day before the cessation date, 2) a follow-up visit 2 weeks after the cessation date, 3) a letter 3 weeks after the cessation date, 4) a second follow-up visit 2 months after the cessation date, and 5) a final evaluation that was carried out after 6 months. At the 6-month follow-up, the smoking cessation incidence was 17.0% in the intervention group compared with 2.3% in the usual care group, which was a 14.7% difference (95% CI 8.2-21.3%). Among participants who continued smoking, a significant reduction was evident in the average cigarette consumption at the 6-month follow-up. The mean number of cigarettes per day decreased from 20.0 at baseline to 15.5 at 6 months for the experimental group versus from 19.7 to 18.1 for the control group ($P < 0.01$).[95]

Motivational interviewing

Motivational Interviewing (MI) is a well-known, scientifically tested method of counselling clients developed by Miller and Rollnick and viewed as a useful intervention strategy in the treatment of lifestyle problems and disease. MI is a directive patient-centred style of counselling, designed to help people to explore and resolve ambivalence about behaviour change. A Cochane review concluded that motivational interviewing may assist people to quit smoking. [99] 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. Another review assessed the evidence and gaps in the literature for MI interventions and outcomes in adults with type 2 DM.[100] The authors concluded that behaviour-specific MI interventions may positively influence study outcomes. Assessment of MI intervention fidelity will enhance treatment integrity and claims for validity.[100]

A study carried out in the US had the purpose to evaluate the impact of a tobacco cessation intervention using MI on smoking cessation rates during diabetes self-management training (DSMT).[94] A randomized controlled trial was conducted with subjects recruited from an on going type 2 DM adult education program at a large diabetes center. A total of 114 subjects were randomized to intervention (n=57; face-to-face MI plus telephone counselling and offer of medication) or standard care (n=57). Outcome measures included tobacco cessation rates, mean number of cigarettes smoked, HgA1C, weight, blood pressure, and lipids. Intensive intervention using MI integrated into a standard DSMT program resulted in a trend toward greater abstinence at 3 months of follow-up in those receiving the intervention. However, this same trend was not observed at 6 months. The addition of this structured smoking cessation intervention did not negatively affect either diabetes education or other measures of diabetes management, including HgA1C values. However, an intervention of moderate intensity for smoking cessation was no more effective than usual care in assisting patients with tobacco cessation after 6-month follow-up. Whether a more intensive intervention, targeting patients expressing a readiness to discontinue tobacco use, and/or a longer duration or a more cumulative effect of treatment will be more effective must be evaluated.[94]

A study evaluated an intervention programme using MI on smoking cessation in patients with DM in seventeen primary health care centres in Sweden.[93] The participants were daily smokers with DM, 30-75 years of age (n=241 intervention group and 171 control group). In the intervention centres, nurses with education in diabetes were given one half-day of training in MI and smoking cessation. An invitation to participate in a smoking cessation group was mailed to patients from the intervention centres followed by a telephone call from the patient's diabetic nurse. The intervention program consisted of eight 45-60 minute group sessions in a two-month period led by nurses with special education in smoking cessation which addressed motivation to stop smoking, and advice on how to break the habit and how to prevent relapse. Pharmacological treatment (NRT or Bupropion was recommended). After the group treatment, patients received individual support and follow-up by telephone calls 3, 6, and 12 months after the quit day. Twenty-one percent of the smokers accepted group treatment. After 12 months, 20% (42/211) in the intervention centres reported that they had stopped smoking and 7% (10/140) in the control centres; 40% (19/47) of the smokers who had participated in group treatment reported that they had stopped smoking.[93]

2.3.2 Setting Specific Interventions

Primary care and out-patient diabetes settings

The monitoring and treatment of patients with type 2 DM is often performed by primary care providers and/or by specialists, the situation varying very much between countries.[51,98] Diabetic patients will meet with health care professionals more frequently than other groups of the population, making these important settings for identifying and intervening with tobacco users.

A study performed among male patients (n=71) recruited from two referral diabetes clinics in Yogyakarta Province, Indonesia involved two interactive smoking cessation interventions: doctor's advice and visual representation of how tobacco affects DM (DA) and DA plus direct referral to a cessation clinic (CC).[91] At 6 months follow-up, DA and CC groups had abstinence rates of 30% and 37%, respectively. Of those continuing to smoke, most reported an attempt to quit or reduce smoking (70% in DA and 88% in CC groups). Patients in both groups had an increased understanding of smoking-related harm and increased motivation to quit smoking. The authors conclude that the study demonstrates the feasibility of disease-centred doctors' messages about smoking cessation for patients with DM, supported by the presence of a CC motivating clinicians to routinely give patients cessation messages.[91]

While most interventions for smoking cessation are delivered by physicians, there are also examples of counselling interventions delivered by nurses or inter-disciplinary teams.[79-88] For instance, studies from Sweden and India found that culturally sensitive diabetic specific cessation counselling sessions, delivered by a non-doctor health professional, was an effective method for encouraging smoking cessation.[87,88,93]

Irrespective of the health professional who delivers the cessation message, several studies underline the importance of using health care professionals who have appropriate training and experience in smoking cessation as well as high quality implementation of the intervention protocol.[87,89,95]

Hospital-based Interventions

Smokers with co-morbid medical conditions such as cancer, cardiac disease, COPD, diabetes, and asthma are important to target for tobacco use treatments, given the role that smoking plays in exacerbating these conditions. Hospitalization often provides a "teachable moment" in which receptivity to quitting smoking increases in particular when the reason for hospitalization is a smoking-related disease. Integrating tobacco treatment into chronic disease management plans can be an effective and efficient way to deliver tobacco use interventions to these populations.[84]

A longitudinal study conducted in the US compared 6-month post-hospitalization tobacco cessation rates among in-patient veterans with and without diabetes who used tobacco in the past month (n=496, mean age 55.2 years, 62% Caucasian).[101] Twenty-nine percent had co-morbid diabetes. A total of 18.8% of patients with diabetes reported tobacco cessation at 6 months compared with 10.9% of those without diabetes (p=0.02). Cotinine-verified cessation rates were 12.5% vs. 7.4% in the groups with and without diabetes, respectively (p=0.07). Controlling for psychiatric co-morbidities, depressive symptoms, age, self-rated health and nicotine dependence, the multivariable-adjusted logistic regression showed that patients with diabetes had three times higher odds of 6-month cotinine-verified tobacco cessation as compared with those without diabetes (OR 3.17; p=0.005). The authors concluded that post-hospitalization rates of smoking cessation are high among those with diabetes and intensive tobacco cessation program may increase these cessation rates further.[101]

Motivating health professionals to get involved in smoking cessation advice and counselling remains a continuous challenge. A study examined the impact of a pay-for-performance incentive in the United Kingdom introduced in 2004 as part of the new general practitioner contract to improve support for smoking cessation and to reduce the prevalence of smoking among people with chronic diseases such as diabetes.[80] The study performed a population-based longitudinal study of the recorded delivery of cessation advice and the prevalence of smoking using electronic records of patients with diabetes obtained from participating general practices.80 The survey was carried out in an ethnically diverse part of southwest London before (June–October 2003) and after (November 2005–January 2006) the introduction of a pay-for performance incentive. The results show that significantly more patients with diabetes had their smoking status ever recorded in 2005 than in 2003 (98.8% v. 90.0%; p<0.001). The proportion of patients with documented smoking cessation advice also increased significantly over this period, from 48.0% to 83.5% (p<0.001). The prevalence of smoking decreased significantly from 20.0% to 16.2% (p<0.001). The reduction over the study period was lower among women (adjusted odds ratio (AOR 0.71, 95% CI 0.53–0.95) but was not significantly different in the most and least affluent groups. In

2005, smoking rates continued to differ significantly with age (10.6-25.1%), sex (women, 11.5%; men, 20.6%) and ethnic background (4.9-24.9%). The authors concluded that the introduction of a pay-for-performance incentive in the United Kingdom increased the provision of support for smoking cessation and was associated with a reduction in smoking prevalence among patients with diabetes in primary health care settings. Health care planners in other countries may wish to consider introducing similar incentive schemes for primary care physicians. Research from Sweden found that a computerized medical record with registration of diabetes diagnoses and smoking status was an effective method for the identification of diabetics who use tobacco who might be contacted later on by health care professionals in order to receive an invitation to participate in smoking cessations programs.[102]

Quit lines

Evidence-based telephone quit lines can support quitting, but have not been studied adequately among patients with chronic diseases such as diabetes.[103] A study from the US investigated the use and effectiveness of quit lines among diabetic patients. A telephone based follow-up survey was performed among participants (enrolled between May – September 2008 from the Washington State Tobacco Quit Line) with and without diabetes 7 months after the enrolment in the quit line. They received one 30-minutes telephone counselling, mailed self-help materials, referral to community based smoking cessation facilities and also received 1-5 follow-up calls. The results show that the enrolment of diabetic patients in the quit line was higher than their proportion in the general population. Quit lines for those with and without diabetes did not differ significantly (24.3% vs. 22.5%). No significant differences existed between the two groups regarding weight gain, independent of smoking status. Weight gain was a significant correlate of continuous smoking, regardless of diabetic status. The authors conclude that quit lines are effective for diabetic patients, but tailored interventions which address weight concerns during cessation are needed.[103]

Technology-based interventions

Many DM patients use communication technologies including the internet, social media, and mobile phones. A major advantage of technology-based approaches to intervention is that these technologies are widely available and allow for easy intervention targeting. Different computer tailoring programs mainly tested in developed countries proved to be effective for smoking cessation in the general population of tobacco users.[104-110] Moreover, computer-based expert systems have been used in clinical settings, in conjunction with motivational counselling, to successfully prevent smoking and induce cessation.[107,108] Technology-based resources (e.g., web sites, text messaging support) can also be delivered as an adjunct to office visits to assist smokers with quitting.

Despite the potential of technology-based intervention no results are reported with regard to effects of these types of interventions on smoking cessation in DM patients.

RECOMMENDATIONS:

- Smoking cessations interventions that are implemented in primary or/and secondary health care by different members of the health care team may have a beneficial effect on smoking cessation among diabetic patients, however the overall number of trials is limited (Level of Evidence B).
- Further research is needed to explore the role of different approaches for counselling for smoking cessation in clinical care using trial designs with follow-up extending to at least 1 year.

2.4 Pharmacological Interventions

Approved pharmacotherapies for smoking cessation that have also been recommended as first-line treatments include various forms of nicotine replacement therapy (NRT), bupropion and varenicline. There is very little data on the efficacy of these pharmacotherapies in individuals with DM.[56,57]

2.4.1 Nicotine Replacement Therapy (NRT)

NRT is available in the form of the long-acting patch, and short-acting gum, inhaler, spray and lozenge. NRT has been shown to double quit rates in the general population of tobacco users and triple quit rates when two forms of NRT are used in combination.[84,85] NRT is used to assist with reducing cravings and withdrawal symptoms related to quitting. NRT dosing is gradually reduced over time.[84,85]

The package insert for Nicorette Nasal spray, Nicorette Inhaler, Nicorette patches, Nicorette gum states that patients with diabetes should be advised to monitor their blood sugar levels more closely than usual when first using NRT products, as catecholamines released by nicotine can affect carbohydrate metabolism.[56] A study including high-nicotine-dependent (time to first cigarette of the day <30 minutes after waking) participants with pre-existing underlying medical conditions found that use of NRT (4 mg lozenge and 4mg gum) demonstrated an acceptable safety profile for up to 12 weeks of treatment in patients with DM as well as other underlying medical conditions (i.e. heart disease and hypertension not controlled by medication).[111]

2.4.2 Bupropion

Bupropion is a non-nicotine therapy for smoking cessation available in tablet form by prescription only which has been shown to be effective in increasing rates of smoking abstinence in the general population of tobacco users.[84,85] The prescribing information for bupropion states that this drug may not be appropriate for use in patients with diabetes treated with hypo-glycaemic agents or insulin due to a risk of seizure.[56] At present, no large-scale clinical trials reporting the efficacy of bupropion in patients with diabetes have been published.

2.4.3 Varenicline

Varenicline is a partial agonist of the α4β2 nicotinic acetylcholine receptor, offering a two-pronged approach to treating the addiction: as a partial agonist of the nicotinic receptor, this drug reduces the symptoms of nicotine withdrawal, while it simultaneously blocks some of its reinforcing effects. Varenicline produces approximately fifty percent (50%) of the receptor stimulation provided by nicotine, and blocks the effects of nicotine inhaled from cigarette use.[112]

There is strong randomized controlled trial evidence that varenicline increases rates of smoking abstinence among the general population of tobacco users and has found to be superior to both NRT and bupropion.[84,85] There are however, no long-term studies examining the efficacy of varenicline specifically in DM patients.

The package insert for varenicline (Champix or Chantix) advises that dose adjustment of the drug may be necessary in patients taking insulin due to potential pharmacokinetic and pharmacodynamic changes that may occur during smoking cessation.[56] There is one case report that indicates that varenicline may induce severe hypoglycaemia in type 1 DM. The author of this report suggested that patients with diabetes attempting to quit smoking with the aid of varenicline should be carefully monitored for blood glucose levels until further investigation of this population has taken place.[113] Smoking cessation improves insulin sensitivity, which may also trigger a hypo-glycaemic event. The issue of safety of such treatments is partly addressed in an on-going trial of varenicline for smoking cessation in diabetes.[114] Monitoring of blood glucose levels in patients with diabetes should be part of routine care.[56]

RECOMMENDATIONS:

- At present there are no large-scale clinical trials reporting the efficacy and safety of NRT, bupropion or varenicline in patients with diabetes. There is however no evidence to mitigate the use of first-line quit smoking medications (NRT, bupropion and varenicline) among diabetic patients (Level of Evidence C).
- Due to the increased risk of seizure bupropion is not recommended for use among DM patients using hypo-glycaemia agents or insulin (Level of Evidence C).
- Closer monitoring of blood sugar levels when first using quit smoking medications is recommended and adjustment of medication may be necessary (Level of Evidence B).

2.5 Cost-effectiveness

A systematic review published in 2010 synthesized the cost-effectiveness (CE) of interventions to prevent and control DM, its complications, and comorbidities.[115] CEs were classified as cost saving (more health benefit at a lower cost), very cost-effective ($25,000 per life year gained [LYG] or quality-adjusted life year [QALY]), cost-

effective ($25,001 to $50,000 per LYG or QALY), marginally cost-effective ($50,001 to $100,000 per LYG or QALY), or not cost-effective ($100,000 per LYG or QALY).[115] Fifty-six studies from 20 countries met the inclusion criteria; out of these one study investigated the cost-effectiveness of smoking cessation among type 2 DM newly diagnosed patients from the US aged 25 to 84 in comparison with those receiving standard care.[115] Authors concluded interventions counselling and treatment for smoking cessation compared with no counselling and treatment was cost-effective.[115]

TABLE 4: Interventions proven to be very cost-effective for the management of Diabetes

1	Intensive lifestyle interventions to prevent type 2 diabetes among persons with impaired glucose tolerance compared with standard lifestyle recommendations;
2	Universal opportunistic screening for undiagnosed type 2 diabetes in African Americans between 45 and 54 years old;
3	Ontensive glycemic control as implemented in the UK Prospective Diabetes Study in persons with newly diagnosed type 2 diabetes compared with conventional glycemic control; 4) statin therapy for secondary prevention of cardiovascular disease compared with no statin therapy;
4	Counselling and treatment for smoking cessation compared with no counselling and treatment;
5	Annual screening for diabetic retinopathy and ensuring treatment in persons with type 1 diabetes compared with no screening;
6	Annual screening for diabetic retinopathy and ensuring treatment in persons with type 2 diabetes compared with no screening;
7	Immediate vitrectomy to treat diabetic retinopathy compared with deferred vitrectomy.

Source: Li et al.,(2010)[115]

RECOMMENDATION

- Future research should focus on investigating the cost-effectiveness of smoking cessation interventions for patients with both type I and type 2 DM.

REFERENCES

1. American diabetic Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010 ; 33(Suppl 1): S62–S69.
2. Pan A, Wang Y, Talaei M, Hu FB. Relation of Smoking With Total Mortality and Cardiovascular Events Among Patients With Diabetes Mellitus A Meta-Analysis and Systematic Review. Circulation 2015 published online before print doi: 10.1161/CIRCULATIONAHA.115.017926.
3. Kanavos P, van den Aardweg, Schurer W. Diabetes expenditure, burden of disease and management in 5 EU countries, 2012. http://www.lse.ac.uk/LSEHealthAndSocialCare/research/LSEHealth/MTRG/LSEDiabetesReport26Jan2012.pdf Accessed April 2017.
4. U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A report of the Surgeon General. http://www.surgeongeneral.gov/library/reports/50-years-of-progress. Accessed December 2016.
5. The Interact consortium. Smoking and Long-Term Risk of Type 2 Diabetes: The EPICInterAct Study in European Populations. Diabetes Care 2014; 37:3164–3171.
6. Pan A, Wang Y, Talaei M, Hu FB, Wu T. Relation of active, passive, and quitting smoking with incident type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2015; 3: 958–67.
7. Zhang L, Curhan GC, Hu FB, Rimm EB, and JP Forman. Association Between Passive and Active Smoking and Incident Type 2 Diabetes in Women. Diabetes Care 2011 Apr; 34(4): 892-897. https://doi.org/10.2337/dc10-2087
8. Wei X, Meng E., and S Yu. A meta-analysis of passive smoking and risk of developing Type 2 Diabetes Mellitus. Diabetes Research and Clinical Practice 2015; 107(1): 9–14.
9. Sun K, Liu D, Wang C, Ren M, Yang C, and L Yan. Passive smoke exposure and risk of diabetes: a meta-analysis of prospective studies. Endocrine 2014; 47(2): 421-427.
10. Houston TK, Person SD, Pletcher MJ, Liu K, Iribarren C, CI Kiefe. Active and passive smoking and development of glucose intolerance among young adults in a prospective cohort: CARDIA study. BMJ 2006; 332:1064. doi: https://doi.org/10.1136/bmj.38779.584028.55
11. Rosengren A, Welin L, Tsipogianni A, Wilhelmsen L. Impact of cardiovascular risk factors on coronary heart disease and mortality among middle aged diabetic men: a general population study. BMJ 1989;299:1127–31.
12. Ostgren CJ, Lindblad U, Melander A, Rastam L. Survival in patients with type 2 diabetes in a Swedish community: Skaraborg hypertension and diabetes project. Diabetes Care 2002;25:1297–302.
13. Nilsson PM, Cederholm J, Eeg-Olofsson K,

et al. Smoking as an independent risk factor for myocardial infarction or stroke in type 2 diabetes: a report from the Swedish National Diabetes Register. Eur J Cardiovasc Prev Rehabil 2009;16: 506–12.
14. Morrish NJ, Stevens LK, Fuller JH, Jarrett RJ, Keen H. Risk factors for macrovascular disease in diabetes mellitus: the London follow-up to the WHO MultinationalStudy of Vascular Disease in Diabetics. Diabetologia 1991;34:590–4.
15. Turner RC, Millns H, Neil HAW, Stratton IM, Manley SE, Matthews DR, et al. Riskfactors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23). BMJ 1998;316:823–8.
16. Kothari V, Stevens RJ, Adler AI, et al. UKPDS 60: risk of stroke in type 2 diabetes estimatedby the UK Prospective Diabetes Study risk engine. Stroke 2002;33:1776–81.
17. Laing SP, Jones ME, Swerdlow AJ, Burden AC, Gatling W. Psychosocial and socioeconomic risk factors for premature death in young people with type 1 diabetes. Diabetes Care 2005;28:1618–23.
18. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–9.
19. Hadden DR, Patterson CC, Atkinson AB, et al. Macrovascular disease and hyperglycaemia:10-year survival analysis in type 2 diabetes mellitus: the Belfast Diet Study. Diabet Med 1997;14:663–72.
20. Palmer CN, Kimber CH, Doney AS, et al. Combined effect of inflammatory gene polymorphisms and the risk of ischemic stroke in a prospective cohort of subjects with type 2 diabetes: a Go-DARTS study. Diabetes 2010;59:2945–8.
21. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Predictors of stroke in middle-aged patients with non-insulin-dependent diabetes. Stroke 1996;27:63–8.
22. Hu G, Jousilahti P, Barengo NC, Qiao Q, Lakka TA, Tuomilehto J. Physical activity, cardiovascular risk factors, and mortality among Finnish adults with diabetes. Diabetes Care 2005;28:799–805.
23. Lutgers HL, Gerrits EG, Sluiter WJ, et al. Life expectancy in a large cohort of type 2 diabetes patients treated in primary care (ZODIAC-10). PLoS One 2009;4:e6817.
24. Muhlhauser I, Overmann H, Bender R, Jorgens V, Berger M. Predictors of mortality and end-stage diabetic complications in patients with Type 1 diabetes mellitus on intensified insulin therapy. Diabet Med 2000;17:727–34.
25. Rossing P, Breum L, Major-Pedersen A, et al. Prolonged QTc interval predicts mortality in patients with Type 1 diabetes mellitus. Diabet Med 2001;18:199–205.

REFERENCES

26. de Fine ON, Siersma V, Nielsen AB, Hansen LJ, Rosenvinge L, Mogensen CE. Predictors of mortality of patients newly diagnosed with clinical type 2 diabetes: a 5-year follow up study. BMC Endocrinol Disord 2010;10:14.
27. Muggeo M, Zoppini G, Bonora E, et al. Fasting plasma glucose variability predicts 10-year survival of type 2 diabetic patients: the Verona Diabetes Study. Diabetes Care 2000;23:45–50.
28. Faglia E, Favales F, Calia P, et al. Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary heart disease: 5-year follow-up report from the Milan Study on Atherosclerosis and Diabetes (MiSAD). Diabetes Care 2002;25:2032–6.
29. Bo S, Ciccone G, Rosato R, et al. Renal damage in patients with Type 2 diabetes: a strong predictor of mortality. Diabet Med 2005;22:258–65.
30. Giorda CB, Avogaro A, Maggini M, et al. Incidence and risk factors for stroke in type 2 diabetic patients: the DAI study. Stroke 2007;38:1154–60.
31. Zoppini G, Targher G, Negri C, et al. Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients. Diabetes Care 2009;32:1716–20.
32. Mata-Cases M, De Prado-Lacueva C, Salido-Valencia V, et al. Incidence of complications and mortality in a type 2 diabetes patient cohort study followed up from diagnosis in a primary healthcare centre. Int J Clin Pract 2011;65:299–307.
33. Soedamah-Muthu SS, Chaturvedi N, Toeller M, et al. Risk factors for coronary heart disease in Type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study. Diabetes Care 2004;27:530–7.
34. Iversen MM, Tell GS, Riise T, et al. History of foot ulcer increases mortality among individuals with diabetes: ten-year follow-up of the Nord-Trondelag Health Study, Norway. Diabetes Care 2009;32:2193-9.
35. Joergensen C, Gall MA, Schmedes A, Tarnow L, Parving HH, Rossing P. Vitamin D levels and mortality in type 2 diabetes. Diabetes Care 2010;33:2238-43.
36. Moy CS, LaPorte RE, Dorman JS, et al. Insulin-dependent diabetes mellitus mortality. The risk of cigarette smoking. Circulation 1990;82:37-43.
37. Ford ES, DeStefano F. Risk factors for mortality from all causes and from coronary heart disease among persons with diabetes. Findings from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Am J Epidemiol 1991;133:1220-30.
38. Al-Delaimy WK, Manson JE, Solomon CG, et al. Smoking and risk of coronary heart disease among women with type 2 diabetes mellitus.

Arch Intern Med 2002;162: 273-9.
39. Al-Delaimy WK, Willett WC, Manson JE, Speizer FE, Hu FB. Smoking and mortality among women with type 2 diabetes: the Nurses' Health Study cohort. Diabetes Care 2001;24:2043-8.
40. Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Arch Intern Med 2005;165:2114–20.
41. Miller RG, Prince CT, Klein R, Orchard TJ. Retinal vessel diameter and the incidence of coronary artery disease in Type 1 diabetes. Am J Ophthalmol 2009;147:653–60.
42. Brown C, Leith J, Dickerson F, et al. Predictors of mortality in patients with serious mental illness and co-occurring type 2 diabetes. Psychiatr Res 2010;177:250–4.
43. Nelson KM, Boyko EJ, Koepsell T. All-cause mortality risk among a national sample of individuals with diabetes. Diabetes Care 2010;33:2360–4.
44. Florkowski CM, Scott RS, Coope PA, Moir CL. Predictors of mortality from type 2 diabetes mellitus in Canterbury, New Zealand; a ten-year cohort study. Diabetes Res Clin Pract 2001;53:113–20.
45. Matsumoto K, Fujita N, Ozaki M, Tominaga T, Ueki Y, Miyake S. Coexistence of insulin resistance and inflammation effectively predicts cardiac disease but not stroke in Japanese patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2006;74:316–21.
46. Davis TME, Fortun P, Mulder J, Davis WA, Bruce DG. Silent myocardial infarction and its prognosis in a community-based cohort of Type 2 diabetic patients: the Fremantle Diabetes Study. Diabetologia 2004;47:395–9.
47. Norman PE, Davis WA, Bruce DG, Davis TME. Peripheral arterial disease and risk of cardiac death in type 2 diabetes: the Fremantle Diabetes Study. Diabetes Care 2006;29:575–80.
48. Ko GT, So WY, Chan NN, et al. Prediction of cardiovascular and total mortality in Chinese type 2 diabetic patients by the WHO definition for the metabolic syndrome. Diabetes Obes Metab 2006;8:94–104.
49. Yang X, Ma RC, So WY, et al. Impacts of chronic kidney disease and albuminuria on associations between coronary heart disease and its traditional risk factors in type 2 diabetic patients — the Hong Kong diabetes registry. Cardiovasc Diabetol 2007;6:37.
50. Yang X, Kong APS, So WY, et al. Effects of chronic hyperglycaemia on incident stroke in Hong Kong Chinese patients with type 2 diabetes. Diabetes Metab Res Rev 2007;23:220–6.
51. Ian A. MacFarlane. The smoker with diabetes: a difficult challenge. Postgrad Med J 1991;67:928-930.

REFERENCES

52. Bae J. Differences in Cigarette Use Behaviors by Age at the Time of Diagnosis With Diabetes From Young Adulthood to Adulthood: Results From the National Longitudinal Study of Adolescent Health J Prev Med Public Health 2013;46:249-60.
53. Schipf S, Schmidt O, Alte D, et al. Smoking prevalence in Type 2 diabetes: results of the Study of Health in Pomerania (SHIP) and the German National Health Interview and Examination Survey (GNHIES). Diabet Med. 2009;26(8):791-97.
54. Fagarda RH, Nilsson PM. Smoking and diabetes—The double health hazard! Primary care diabetes 2009;3:205–209.
55. Qin R, Chen T, Lou Q, Yu D. Excess risk of mortality and cardiovascular events associated with smoking among patients with diabetes: Meta-analysis of observational prospective studies International Journal of Cardiology 2013;167: 342–50.
56. Tonstad S. Cigarette smoking, smoking cessation, and diabetes. Diabetes Res Clin Pract 2009;85:4–13.
57. Chang SA. Smoking and Type 2 Diabetes Mellitus. Diabetes Metab J 2012; 36:399-403.
58. Biesenbach G, Grafinger P, Janko O, Zazgornik J. Influence of cigarette-smoking on the progression of clinical diabetic nephropathy in type 2 diabetic patients. Clin Nephrol 1997;48:146-50.
59. Chuahirun T, Wesson DE. Cigarette smoking predicts faster progression of type 2 established diabetic nephropathy despite ACE inhibition. Am J Kidney Dis 2002; 39:376-82.
60. Chuahirun T, Khanna A, Kimball K, Wesson DE. Cigarette smoking and increased urine albumin excretion are interrelated predictors of nephropathy progression in type 2 diabetes. Am J Kidney Dis 2003;41:13-21.
61. Guillausseau PJ, Massin P, Charles MA, Allaguy H, Guvenli Z, Virally M, Tielmans D, Assayag M, Warnet A, Lubetzki J. Glycaemic control and development of retinopathy in type 2 dia¬betes mellitus: a longitudinal study. Diabet Med 1998; 15:151-5.
62. Moss SE, Klein R, Klein BE. Cigarette smoking and ten-year progression of diabetic retinopathy. Ophthalmology 1996; 103: 1438-42.
63. Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, Matthews DR. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. Diabetologia 2001; 44:156-63.
64. Chaturvedi N, Stephenson JM, Fuller JH. The relationship between smoking and microvascular complications in the EURODIAB IDDM Complications Study. Diabetes Care 1995; 18:785–92.
65. Eliasson B. Cigarette smoking and diabetes. Prog Cardiovasc Dis. 2003; 45: 405–13.
66. Velilla S, García-Medina J, García-Layana

A, Dolz-Marco R, Pons-Vázquez S, Pinazo-Durán D, Gómez-Ulla F, Arévalo FJ, Díaz-Llopis M, and R Gallego-Pinazo. Smoking and Age-Related Macular Degeneration: Review and Update. J Ophthalmol. 2013; 2013: 895147.

67. Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, and S P Kelly. Smoking and age-related macular degeneration: a review of association. Eye (2005) 19, 935–944. doi:10.1038/sj.eye.6701978
68. Clair C, Cohen MJ, Eichler F, Selby KJ, Rigotti NA. The Effect of Cigarette Smoking on Diabetic Peripheral Neuropathy:A Systematic Review and Meta-Analysis.J Gen Intern Med. 2015; 30(8):1193-203.
69. Hirai FE, Moss SE, Klein BE, Klein R. Severe hypoglycemia and smoking in a long-term type 1 diabetic population: Wisconsin Epidemiologic Study of Diabetic Retinopathy, Diabetes Care 2007; 30:1437–1441.
70. Clair C, Rigotti NA, Porneala B, et al. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. JAMA 2013;309:1014-1021.
71. Lycett D, Nichols L, Ryat R. et all. The association between smoking cessation and glycaemic control in patients with type 2 diabetes: a THIN database cohort study. Lancet Diabetes Endocrinol. 2015;3(6):423-30.
72. Fowler PM, Hoskins PL, McGill M, Dutton SP, Yue DK, Turtle JR. Anti-smoking Programme for Diabetic Patients: The Agony and the Ecstasy. Diabetic Medicine 1989;6: 698–702.
73. Cinciripini PM, Wetter DW, Fouladi RT, Blalock JA, Carter BL,Cinciripini LG et al. The effects of depressed mood on smoking cessation: mediation by post-cessation self-efficacy. J Consult ClinPsychol 2003; 71: 292–301.
74. Solberg LI, Desai JR, O'Connor PJ, Bishop DB, Devlin HM.Diabetic patients who smoke: are they different? Ann Fam Med 2004;2: 26–32.
75. Regber S, Kelly KB. Missed opportunities-adolescents with achronic condition (insulin-dependent diabetes mellitus) describetheir cigarette-smoking trajectories and consider health risks. Acta Paediatr 2007;96:1770-1776.
76. Surís JC. Chronic conditions and adolescence. J Pediatr Endocrinol Metab 2003;16:247-251.
77. Valencia LS, Cromer BA. Sexual activity and other high-risk behaviors in adolescents with chronic illness: a review. J Pediatr Adolesc Gynecol 2000;13(2):53-64.
78. Reynolds K, Liese AD, Anderson AM, Dabelea D, Standiford D, Daniels SR, Waitzfelder B, Case D, Loots B, Imperatore G, Lawrence JM. Prevalence of Tobacco Use and Association between Cardiometabolic Risk Factors and Cigarette Smoking in Youth with Type 1 or Type 2 Diabetes Mellitus . J Pediatr. 2011;158(4):594–601.

REFERENCES

79. Schauer GL, Halperin C, Manc LA. Health professional advice for smoking and weight in adults with and without diabetes: findings from BRFSS Journal of Behavioral Medicine 2013;36: 10-19.
80. Millett C, Gray J, Saxena S, Netuveli G, Majeed A. Impact of a pay-for-performance incentive on support for smoking cessation and on smoking prevalence among people with diabetes CMAJ. 2007;176:1705-10.
81. Jansink, R, Braspenning J, van der Weijden T, Elwyn G, Grol R.Primary care nurses struggle with lifestyle counseling in diabetes care: a qualitative analysis BMC Family Practice 2010; 11:41.
82. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care 2013; 36:11–66.
83. American Diabetes Association Position Statement: Standards of Medical Care in Diabetes—2016. Diabetes Care 2016;39(Suppl. 1):S1–S112.
84. US Department of Health and human Services. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. http://www.ahrq.gov/sites/default/files/wysiwyg/professionals/clinicians-providers/guidelines-ecommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf. Accessed December 2015.
85. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD009329. DOI: 10.1002/14651858.CD009329.pub2.
86. Mays D, Streisand R, Walker LR, Prokhorov AV, Tercyak KP. Cigarette smoking among adolescents with type 1 diabetes: Strategies for behavioural prevention and intervention. Journal of Diabetes and Its Complications 2012; 26:148–153.
87. Thankappan KR1, Mini GK, Daivadanam M, Vijayakumar G, Sarma PS, Nichter M.Smoking cessation among diabetes patients: results of a pilot randomized controlled trial. Diabetes Care. 2014;37(12):e256–e257.
88. Thankappan KR, Mini GK, Hariharan M, Vijayakumar G, Sarma PS, Nichter. M. Smoking Cessation Among Diabetic Patients in Kerala, India: 1-Year Follow-up Results From a Pilot Randomized Controlled Trial. Journal of Clinical Nursing 2015;24:2545–2553.
89. Nagrebetsky A, Brettell R, Roberts N, Farmer A. Smoking cessation in adults with diabetes: a systematic review and meta-analysis of data from randomised controlled trials. BMJ Open 2014;4:e004107.
90. Perez-Tortosa S, Roig L, Manresa JM, Martin-Cantera C. Continued smoking abstinence in diabetic patients in primary care: A cluster randomized controlled

multicenter study. Diabetes res clinic practice 2015;107:9 4 –1 0 3.
91. Ng N, Nichter M, Padmawati RS, Prabandari YS, Muramoto M, Nichter M. Bringing smoking cessation to diabetes clinics in Indonesia. Chronic Illn. 2010;6(2):125-35.
92. Davies MJ, Heller S, Skinner TC, et all. Effectiveness of the diabetes education and self-management for on going and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cluster randomised controlled trial. BMJ. 2008; 336:491-5.
93. Persson LG, Hjalmarson A: Smoking cessation in patients with diabetes mellitus: results from a controlled study of an intervention programme in primary healthcare in Sweden. Scand J Prim Health Care 2006;24:75-80.
94. Hokanson JM, Anderson RL, Hennrikus DJ, Lando HA, Kendall DM:Integrated tobacco cessation counseling in a diabetes self-managementtraining program: a randomized trial of diabetes and reduction of tobacco. Diabetes Educ 2006; 32:562-570.
95. Canga N, De IJ, Vara E, Duaso MJ, Ferrer A, Martinez-Gonzalez MA: Intervention study for smoking cessation in diabetic patients: a randomized controlled trial in both clinical and primary care settings. Diabetes Care 2000; 23:1455-1460.
96. Sawicki PT, Didjurgeit U, Muhlhauser I, Berger M. Behaviour therapy versus doctor's anti-smoking advice in diabetic patients, J. Intern. Med. 1993;234:407–409.
97. Hartmann-Boyce J, Stead LF, Cahill K, Lancaster T. Efficacy of interventions to combat tobacco addiction: Cochrane update of 2012 reviews Addiction. 2013;108(10):1711-21.
98. Albareda M, Sánchez L, González J, Viguera J, Mestrón A, Vernet A, Vila L. Results of the application of the American Diabetes Association guidelines regarding tobacco dependency in subjects with diabetes mellitus. Metabolism 2009;58(9):1234-8.
99. Lindson-Hawley N, Thompson TP, Begh R. Motivational interviewing for smoking cessation. Cochrane Database Syst Rev. 2015;3:CD006936.
100. Ekong G, Kavookjian J. Motivational interviewing and outcomes in adults with type 2 diabetes: A systematic review 2015; pii:S0738-3991(15)30137-3.
101. Duffy SA, Munger A, Karvonen-Gutierrez CA, et al. Post-discharge tobacco cessation rates among hospitalized US veterans with and without diabetes. Diabet Med 2012;29:e96–101.
102. Persson LG, Lindstro¨m K, Lingfors H. Quality improvement in primary health care using computerised journal, exemplified by a smoking cessation programme for diabetic patients. Scand J Prim Health Care 2000;18:252-3.

REFERENCES

103. Schauer G, Bush T, Cerutti B, et al. Use and effectiveness of quitlines for smokers with diabetes: Cessation and weight outcomes, Washington State Tobacco Quitline, 2008. Preventing Cronic Diseases 2013;10:1-13.
104. Lustria ML, Noar SM, Cortese J, Van Stee SK, Glueckauf RL, Lee J.A meta-analysis of web-delivered tailored health behavior change interventions. J Health Commun 2013;18:1039-1069.
105. Civljak, M., Sheikh, A., Stead, L.F. (2010). Internet-based interventions for smoking cessation. Cochrane Database Syst Rev, 9,CD007078.
106. Shahab L, McEwen A. Online support for smoking cessation: a systematic review of the literature. Addict. 2009; 104: 1792-804.
107. Smit ES, de Vries, H, Hoving C. Effectiveness of a Web-Based Multiple Tailored Smoking Cessation Program: A Randomized Controlled Trial Among Dutch Adult Smokers J Med Internet 2012;14: e82.
108. Smit ES, Evers SM, de Vries H., Hoving, C. Cost-effectiveness and cost-utility of Internet-based computer tailoring for smoking cessation. J Med Internet Res 2013;15: e57.
109. Hollis JF, Polen MR, Whitlock EP et al. (2005). Teen reach: outcomes from a randomized, controlled trial of a tobacco reduction program for teens seen in primary medical care. Pediatrics 2005;115: 981–989.
110. Pbert L, Flint A J, Fletcher KE, Young MH, Druker S, DiFranza JR. Effect of a pediatric practice-based smoking prevention and cessation intervention for adolescents: a randomized, controlled trial. Pediatrics 2008;121: e738–e747.
111. Marsh HS, Dresler CM, Choi JH, Targett DS, Gamble ML, Strahs KR. Safety profile of a nicotine lozenge compared with that of nicotine gum in adult smokers with underlying medical conditions: a 12-week, randomized, open-label study, Clin. Ther. 2005; 27:1571–1587.
112. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR; Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006;296(1):47-55.
113. Kristensen PL, Pedersen-Bjergaard U, Thorsteinsson B. Varenicline may trigger severe hypoglycaemia in type 1 diabetes, Diabetes Med 2008;25(5):625-6.
114. Efficacy and safety of smoking cessation with varenicline tartrate in diabetic smokers: (DIASMOKE).http://clinicaltrials.gov/show/NCT01387425 25.
115. Li R, Zhang P, Barker L. Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus:a systematic review.Diabetes Care. 2010;33(8):1872-94. ■

4.

SMOKING CESSATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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About this Guideline

This special chapter of the European Tobacco Treatment Guideline is intended to summarize evidence regarding the health risk associated with tobacco use in patients with chronic obstructive pulmonary disease (COPD) as well as effective approaches to supporting cessation in this important population of tobacco users.

Within the chapter clinical practice recommendations are presented for health care professionals working with COPD. The GRADE evidence grading system has been used to rate the quality of evidence supporting each of the recommendations. The evidence grading scale reflects the type, quality and quantity of available evidence supporting the guideline recommendation. GRADE uses 4 evidence grading categories: 'high', 'moderate', 'low', 'very low' (see table below). The level of evidence grading appears in brackets at the end of each recommendation statement.

GRADE - Evidence Grading Categories:

CODE	QUALITY OF EVIDENCE	DEFINITION
A	High	– Further research is very unlikely to change our confidence in the estimate of effect. – Several high-quality studies with consistent results. – In special cases: one large, high-quality multi-center trial
B	Moderate	– Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. – One high-quality study. – Several studies with some limitations.
C	Low	– Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. – One or more studies with severe limitations.
D	Very Low	– Any estimate of effect is very uncertain. – Expert opinion. – No direct research evidence. – One or more studies with very severe limitations.

EXECUTIVE SUMMARY

SMOKING CESSATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)HEALTH EFFECTS OF SMOKING IN PREGNANCY

Health Effects of Smoking in COPD patients

- Tobacco use is the main risk factor for the development of COPD. Tobacco users have a 50% greater probability of developing COPD during their lifetime.
- Second-hand smoke exposure is associated with reduced health status and increased exacerbations among COPD patients. Research has documented a link between passive smoking in childhood and the development of COPD in adulthood.

Health Benefits of Smoking Cessation

- Smoking cessation is the most effective treatment for reducing the rate of COPD progression among patients who smoke and is highly cost-effective.
- Smoking cessation is beneficial at any time for COPD smokers, and has been shown to: slow COPD progression, reduce exacerbation rates, increase effectiveness of COPD treatments, and improve overall quality of life. Respiratory symptoms ameliorate after 3-9 months after quitting smoking and lung function may increase by 10%.

Benefits of cessation in COPD smokers

- > Decreased prevalence of respiratory symptoms
- > Reduced number of hospitalizations
- > Respiratory symptoms improve in the first year post-cessation
- > Annual FEV1 decline is reduced, with a cumulated decline in 5 years of 72ml following cessation compared to 301ml in continuing smokers
- > Reduction in all-cause mortality
- > The most effective measure to reduce COPD progression
- > Improves responses to bronchodilator drugs and to inhaled corticosteroids
- > Reduces bronchial infections

Source: Jimenez Ruiz and Undermer et.al., 2014[1]

Profile of Tobacco Users with COPD

- Tobacco users with COPD smoke more, inhale deeper and are more addicted to tobacco than the general population of tobacco users. In fact, exhaled carbon monoxide (CO) concentration among smokers with COPD has been found to be higher than in the general population.
- Smokers with COPD find it more difficult to stop using tobacco than the general population of tobacco users. COPD disease pattern co-existence of depression, anxiety, etc. is associated with a lack of motivation and self-confidence for quitting, thus reducing the odds of quitting smoking.
- Understanding these differences and tailoring cessation interventions may assist with increasing effectiveness of smoking cessation treatments among smokers with COPD.

Smoking Cessation Interventions in COPD patients

- Smoking cessation interventions should be integrated into routine care of COPD patients who smoke, in both primary care and specialist settings. Hospitalizations, exacerbations and regular check-ups constitute ideal moments to arrange smoking cessation interventions.

- All patients should have a full assessment of smoking history including nicotine addiction, triggers and routines. Biochemical validation can serve as an instrument for assessing smoking and for increasing motivation of COPD patients to quit smoking. Exhaled air carbon monoxide (CO) can be used in clinical settings to assess smoking status and to monitor smoking cessation. "Lung Age" may also be used as a secondary strategy for intervening with smokers.
- The combination of counseling and pharmacotherapy is more effective for addressing nicotine dependence among COPD patients than either alone.
- COPD patients', in particular those who report high levels of nicotine dependence, have more difficulty with quitting than the general population of tobacco users and will require structured and intensive smoking cessation support in order to quit.
- Available pharmacotherapy with proven effectiveness for supporting cessation among COPD patients who smoke include: Bupropion and Nortryptyline, Varenicline and Nicotine Replacement Therapy. High dose NRT, Varenicline and Bupropion is recommended for COPD patients who report moderate to high levels of nicotine addiction as measured by the Fagerstrom Test of Nicotine Dependence. When using NRT, the combination of two types of NRT with different types of delivery is highly recommended. Increasing the length of time that quit smoking medication is used to up to six or twelve months can be effective in increasing abstinence rates in COPD smokers compared to the standard 10 weeks of NRT therapy.
- Frequent follow-up should be provided to support cessation and referral to quit smoking specialist should be considered.

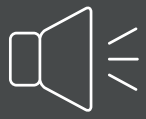
Key Recommendations for Health Professionals:

- Among COPD patients who continue to smoke, smoking cessation is the key clinical intervention for reducing progressive lung destruction and lung function deterioration and should be a clinical priority for all patients (Level of Evidence A).
- Co-habitants and families of COPD patients should be instructed not to expose COPD patients to tobacco smoke and should be included in smoking cessation programs (Level of Evidence D).
- All health care providers who treat COPD patients who smoke should be aware of the specific tobacco use and cessation patterns of this group of patients in order to tailor intervention strategies and increase success with quitting (Level of Evidence D).
- Smoking cessation interventions should be integrated into routine care of COPD patients who smoke, in both primary care and specialist settings (Level of Evidence A).
- Primary care providers, pulmonologists and other health professionals involved in the treatment of COPD

should be trained in evidence-based smoking cessation treatment and be prepared to provide smoking cessation pharmacotherapy and counselling to their COPD patients or may refer them to a colleague trained in smoking cessation (Level of Evidence A).

- A combination of high-intensity counseling and pharmacotherapy is the most effective strategy for treating tobacco use in patients with COPD (Level of Evidence B).
- Exhaled air carbon monoxide (CO) and cotinine are useful non-invasive biomarkers of tobacco smoke exposure and can be used in clinical settings to assess smoking status and to monitor smoking cessation (Level of Evidence A).
- Clinicians overseeing the care of COPD smokers should take the opportunity to assess CO values whenever possible in follow-up visits and use it as a motivational tool to support quit attempts, being at the same time aware of the higher CO levels due to airway inflammatory process (Level of Evidence B).
- The role of "lung age" for increasing patient motivation to quit smoking deserves further investigation (Level of Evidence C).
- A growing body of evidence suggests that majority of COPD patients', in particular those who report high levels of nicotine dependence will require a structured and intensive smoking cessation support in order to quit (Level of Evidence C).
- NRT can be used to support cessation among COPD patients; however standard dosing of NRT among COPD populations has produced lower quit rates than in the general population of smokers (Level of Evidence A).
- High dose NRT is recommended for COPD patients who report moderate to high levels of nicotine addiction as measured by the Fagerstrom Test of Nicotine Dependence. The combination of two types of NRT with different types of delivery is highly recommended (Level of Evidence A).
- Increasing the length of time that NRT is used to up to six or twelve months can be effective in increasing abstinence rates in COPD smokers compared to the standard 10 weeks of NRT therapy (Level of Evidence A).
- For COPD patients with low motivation to quit, NRT may be used to support gradual smoking reduction (Level of Evidence B).
- Varenicline is a first-line quit smoking medication that has been shown to be effective in supporting cessation in smokers with COPD, regardless of disease severity or number of cigarettes smoked (Level of Evidence B).
- Bupropion is an effective aid to support smoking cessation among COPD patients and it is safe to use bupropion in this population of tobacco users (Level of Evidence B).

TOBACCO TREATMENT PROTOCOL – COPD PATIENTS



ASK

ASK about current and former tobacco use (cigs/day & years smoking)
Measure exhaled carbon monoxide of all (COPD patients)
Document in clinical record

NON SMOKER

Assess exposure to second hand smoke and address as appropriate
Assess risk of relapse in recent quitters (< 6 months)

ADVISE

Deliver strong, non-judgmental, personalized ADVICE to quit smoking to all tobacco users and offer support with quitting while in hospital

ASSESS

ASSESS nicotine addiction, past quit attempts, anxiety & depression, readiness/motivation to quit patient is willing to make a quit attempt at this time

READY

ASSIST patient with developing a personalized plan for quitting:
- Provide structured and intensive counselling to support cessation;
- Set quit date, identify triggers and routines and plan for strategies post-quitting;
- Prescribe quit smoking pharmacotherapy: High Dose & Combination NRT, Bupropion or Varenicline
- Provide printed self-help materials

NOT READY

ASSIST
- Provide Motivational Interviewing to enhance motivation to quit;
- Use "Reduce to Quit" Approach with High Dose NRT;
- Provide bio-feedback using "CO" testing or "Lung Age" to enhance Motivation (secondary strategy)

ARANGE

- Provide frequent follow-up counselling support cessation for at least 2-6 months
- Titrate quit smoking medications as appropriate and continue for 12-26 weeks or longer as required
- Consider providing bio-feedback (Lung age & CO levels) to support cessation
- Consider referral to quit smoking specialist

ARANGE

- Provide frequent follow-up to address motivation
- Consider referral to quit smoking specialist

1.0
THE BASIS FOR SMOKING CESSATION FOR COPD PATIENTS

1.1 Introduction

Chronic Obstructive Pulmonary Disease (COPD) has been defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as a preventable and treatable disease, characterized by progressive airflow limitation that is not fully reversible.[2] Individuals with COPD have an abnormal inflammatory response of the lung to noxious particles or gases with some significant extra-pulmonary effects that contribute to the severity of the disease.[2] The airflow limitation experienced in COPD patients is due to chronic obstructive bronchiolitis and loss of elastic recoil caused by destruction of lung parenchyma (emphysema). Patients with COPD also display pathologically distinct structural alterations of the small airways (airway remodeling), as well as systemic inflammation.[3-5]

There is extensive evidence that supports tobacco use as the primary cause of COPD.[6] Since the first U.S. Surgeon General's report in 1964, there has been evidence regarding the harmful effect of tobacco use on respiratory health.[7] This is particularly true for COPD in its two associated clinical presentations: chronic bronchitis and emphysema. In 2014, a valuable review of the respiratory health hazards in relation with smoking was published through collaboration between the European Respiratory Society (ERS) and the UK Centre for Tobacco and Alcohol Studies (UKCTAS), resulting in the website www.smokehaz.eu.[8]

Smoking cessation has been identified as the primary intervention for patients with COPD who use tobacco[9] and has been shown to reduce mortality due to COPD and to improve lung function, whereas oxygen and pharmacological therapy simply reduce the severity of signs and symptoms of the disease.[10]

COPD smokers or former smokers are considered a very high-risk population and urgent action is required to address tobacco use exposure. Additionally, repeated exposure to passive smoking,[10] and many other environmental pollutants and occupational exposures (e.g. grain, flour, coal) contribute to the pathology of COPD.[11]

There are several guidelines and position papers available to guide clinical tobacco dependence treatment, including the US,[12],UK,[13] Canada,[14, 15] and the recently updated European Network for Smoking Prevention's (ENSP) guidelines.[16] While most of the existing guidelines recommend a general approach to treating tobacco use in patients with COPD, a series of materials produced by ERS have focused in particular on smoking cessa-

tion in COPD, and have called for more aggressive and tailored approaches to treatment in this high risk population of tobacco users.[1, 17]

In keeping with the scientific contributions of the ERS and ENSP authoritative guide for treating tobacco dependence,[18] the present guideline is designed specifically for COPD high risk smokers and is intended to enrich European capacity for the treatment of tobacco use and dependence and also to serve as a resource for health care practitioners and respiratory health policy makers.

1.2 COPD – A tobacco induced disease

Tobacco smoking is the main cause of COPD[19] and it is also the main determinant of a poor outcome in those who have the disease.[20, 21] The risk of developing COPD is also greater among former smokers than in non-smokers years after they quit.[22] In a landmark study, Lundback et al. have documented that 50% of smokers eventually develop COPD, as defined according to the GOLD Guidelines.[23] This finding is of major clinical significance and provides a scientific basis for advising smokers that if they continue smoking lifelong, they have at least a one in two chance of developing COPD.[24]

Tobacco use is associated with the deterioration of pulmonary function,[21] an early age of forced expiratory volume (FEV_1) decline,[25] and an accelerated annual decline of FEV_1 in late adulthood.[26] Chronic exposure to cigarette smoke leads to lung inflammation with an increase of inflammatory cells such as macrophages,[27, 28] neutrophils,[29, 30] dendritic cells (DCs),[31, 32] and CD8_T lymphocytes.[33] These cells are capable of releasing inflammatory mediators and proteinases, such as matrix metalloproteinase (MMPs) or neutrophil elastase, which are believed to play a role in the progressive lung destruction in COPD.[34, 35]

According to a systematic review of the literature for detailed information on chemical components in tobacco smoke, lung function and other harmful respiratory effects were attributed to acrylonitrile, ammonia, chromium, cobalt, copper, nickel and m-xylene. Aldehydes and small organic compounds resulting from combustion of organic material are the most responsible for respiratory irritation.[36] There is a non-cancer risk index (NCRI) that can be assessed to establish various non-cancer risks of tobacco smoke and it appears major respiratory irritation NCRI is due to formaldehyde, acetaldehyde and acrolein.[36] Tobacco use is associated with very large rates of exposure to oxidants like peroxyl organic free radicals, N2O, nitric oxide, etc. that trigger inflammatory responses and lead to airway inflammation.[37] Some constituents of cigarette smoke are not yet well studied in experimental research, such as styrene, acetamide, methyl-chloride, etc. or additives that are added to cigarettes in order to increase tobacco addiction. In addition, the large variability in toxins across cigarette brands and their danger of the inhalator risk for inducing a COPD is not well understood.[38]

It is important to highlight that our current knowledge about the causes of COPD is generally based on data from the elderly population in whom the disease is frequent and, in contrast, the risk factors for the early incep-

tion of COPD are still uncertain, as only few surveys have addressed young populations.39 Knowledge of the etiology of the disease has been shown to contribute to a patient's decision to stop smoking. Patients who attribute their respiratory symptoms to smoking are eight times more likely to believe their health will improve by quitting and 6 times more likely to intend quitting.[40]

RECOMMENDATIONS:

- Among COPD patients who continue to smoke, smoking cessation is the key clinical intervention for reducing progressive lung destruction and lung function deterioration and should be a priority for all patients (Level of Evidence A).
- Future research is needed to develop an efficient educational approach to "teach" COPD smokers that COPD is a disease caused and aggravated by continuing smoking.

1.3 Second-hand smoke exposure and risks of COPD

It is well known that cigarette smoke contains approximately 4000 chemicals including 50 proven carcinogens that are delivered either actively, via inhaled air into the lungs, or passively inhaled from the environment where exhaled smoke exists, and it seems therefore logical to foresee the link between COPD and second-hand smoke (SHS).[41, 42] SHS contains respiratory irritants, thus it may adversely influence the clinical course of COPD. In an analysis of cross-sectional data from the UK's annual health survey, based on self-declared passive smoking, Jordan and colleagues have shown a significant dose-response correlation between hours of exposure and increased COPD risk, in terms of clinically significant airway obstruction and symptoms and a two-fold increase COPD risk among never smokers, when exposed > 20 hours per week.[43]

Data from nonsmoking members of the FLOW cohort of COPD were useful in demonstrating the impact of SHS exposure on health status and exacerbations requiring emergency department visits or hospitalization.[44] SHS exposure, measured by a validated survey instrument (hours of exposure during the past week), was associated with poorer health status and greater risk of COPD exacerbation. Being aware of study limitations (potential misclassification of COPD by using medical records review and of self-reported SHS and personal smoking status) authors concluded that COPD patients may comprise a vulnerable population for the health effects of SHS.[44]

A Korean national survey reported increased COPD risk among never smokers exposed to > 6 hours/day of SHS, but concluded observed differences in risk among individuals exposed to SHS to be non-significant, as in the group exposed to SHS for > 6 hours per day, the odds ratio for COPD prevalence was 1.75 (0.47 to 6.59, p = 0.41) after adjusting for variables such as age, gender, previous diagnosis of asthma and tuberculosis, family income and education status. Authors acknowledged limitations of their cross-sectional design study, unable to demonstrate a causal relationship between SHS and COPD, thus could not allow detection of any significance.

As well, they accounted for the possibility of inaccurate recording of exposure by the questionnaires used and urine cotinine validation.[45]

The association between exposure to SHS in childhood and COPD related symptoms in adults has been frequently identified in the literature over the past decade. Children exposed to cigarette smoke in their homes are likely to have lower lung function at their peak than non-exposed children, and lung function decline in early adulthood is associated with COPD later in life.[45-47] In a study on 433 COPD patients versus 325 controls, it was shown that exposure to SHS during childhood was overall a much stronger risk factor than exposure to ETS in adulthood.[42]

Exposure to SHS can be measured by: self-reported indicators of exposure through interviews or questionnaires, measuring tobacco smoke components in the air to which subjects are exposed (environmental measurements) or by measuring concentration of tobacco smoke compounds in the body of the exposed subjects (biomarkers).[48] Such biomarkers for current use in clinical practice are carbon monoxide (CO) concentration in exhaled air, to certify recent, 4-5 hours exposure and cotinine (a metabolite of nicotine) for past, no longer than 3 days exposure. Cotinine is considered the preferred biomarker of SHS exposure, as shown in **Table 1**.

TABLE 1: Published Values of Cotinine in Plasma, Urine, and Saliva* by Exposure Level

Matrix	Unexposed Non-smokers	Passive smokers	Active smokers
Plasma (ng/mL)	0.09-0.7	2-10	>10
Urine (ng/mL)	<10	10-100	>200
Saliva (ng/mL)	0-5, 0.182	5-10	>10

Source: Florescu A.et.al., Values reported by the California EPA Report (2004)1 and Bramer and Kallungal

While there is good evidence to establish increased risk for developing asthma and other respiratory disease and tobacco use, there is need for more research to establish specific risk of passive smoking for COPD.

RECOMMENDATIONS:

- Co-habitants and families of COPD patients should be instructed not to expose COPD patients to tobacco smoke and should be included in smoking cessation programs (Level of Evidence D).
- There is a need for future research to find effective interventions to stop/reduce second-hand smoking exposure in COPD patients.

1.4 Statistics on prevalence and burden of COPD and tobacco use

There are more than one billion smokers in the world, and globally the use of tobacco products is increasing, with the epidemic shifting to the developing world.[49] More than 80% of the world's smokers live in low and middle-income countries. It is estimated that tobacco use kills 5.4 million people a year and accounts for 10% of adult deaths worldwide, with up to 50% of smokers dying from a tobacco-use related disease.[49]

According to the WHO, one hundred million deaths were caused by tobacco in the 20th century, and if current trends continue, there will be up to one billion deaths attributed to tobacco use in the 21st century.[49] Furthermore estimates indicate tobacco related deaths will increase to more than eight million a year by 2030, and 80% of those deaths will occur in developing countries. Trends in increasing/decreasing cigarette consumption are strongly reflected in increasing/decreasing prevalence and progression of COPD. There is growing evidence that the rate of progression of COPD can be reduced when patients at risk of developing the disease stop smoking, while lifelong smokers have a 50% probability of developing COPD during their lifetime. A Norwegian study found that one, in every three, tobacco users with more than 20 pack-years suffered from COPD.[50]

The proportion of people with COPD who continue to smoke has been estimated to be between 32.8% and 70%[51, 52] The prevalence of tobacco use among patients with COPD according to disease severity is: 54% to 77% in mild COPD patients and 38% to 51% in those with severe COPD.[53] Two studies conducted in the general population have documented the association between increased tobacco consumption and daily cigarette consumption among individuals with COPD, compared to non-COPD subjects: 24.2 SD±14.4 vs. 18.5 SD±11.7 cigarettes/day ($p<0.0001$) in a study by Jiménez-Ruiz et al.[54] and 16.3 SD±10 4 vs. 14.8 SD±9.2 cigarettes/day ($p< 0.02$) in a study by Shahab et al.[55] Interestingly, an analysis of mortality specifically in relation to lung function and smoking habits found that the all-cause mortality rate did not differ significantly between former smokers and never smokers, whereas it was increased in current smokers.[56, 57] Results from the Obstructive Lung Disease in Northern Sweden (OLIN) studies and the Copenhagen City Heart Study confirmed that the risk of acquiring COPD according to either British Thoracic Society or GOLD criteria decreased with increasing time since smoking cessation.[58, 59]

RECOMMENDATIONS:

- Additional research is needed to assess impact of tobacco smoking on COPD development and role of smoking cessation in severe stages of COPD

1.5 Benefits of smoking cessation for COPD patients

There is a large body of evidence regarding the benefits of quitting smoking in patients at risk of COPD as well as in individuals diagnosed with COPD. Smoking cessation has been shown to reduce the risk of COPD, improve both the prognosis,[21, 60] and prevent progression of the disease,[61] as well as reduce exacerbations of COPD.[62-64] The risk of developing COPD falls by about half with smoking cessation.[65]

In a review of literature on COPD-related morbidity and mortality (including all-cause mortality) among COPD patients in connection with smoking cessation, it was concluded that even in severe COPD, smoking cessation slows the accelerated rate of lung function decline and improves survival compared with continued smoking.[66] In contrast, reducing smoking does not decrease hospitalization risk for COPD and only a major smoking reduction (at least 85%) allows a mild increase in FEV1.[67]

In addition to proven benefits of smoking cessation on the rate of lung function decline, the Lung Health Study demonstrated that a smoking cessation intervention resulted in the development of fewer symptoms, including dyspnea, cough, sputum production and wheezing.[62] Respiratory symptoms ameliorate after 3-9 months post quitting and lung function may increase by 10%.[68] Tonnesen and colleagues also found smoking cessation improved symptoms such as cough, coughing, shortness of breath and immune response, which leads to fewer respiratory infections to occur.[17] Other important gains from smoking cessation are improved efficacy of oxygen therapy and of COPD inhalator medication, like bronchodilators[26] or inhaled corticosteroids.[69]

Heavy smokers stand to benefit the most from cessation and to lose the most if they continue smoking. Older smokers benefit nearly as much, in terms of improved rates of decline in lung function, as younger smokers. Likewise, smokers with the worst lung function deteriorate most rapidly if they continue smoking; therefore they benefit the most from smoking cessation. Smokers with airflow obstruction benefit from quitting smoking, despite previous heavy smoking, advanced age, poor baseline lung function, or airway hyper responsiveness. (Scanlon et.al, 2000) An improvement in lung function after smoking cessation, such as that experienced by the Lung Health Study participants has been reported by only a few studies.[70] When smokers are counselled to quit smoking, they may explain their unwillingness or inability to quit by claiming that they are too old to benefit from quitting, that they smoke too heavily and cannot quit, or that they have already damaged their lungs irreparably. The most important benefits of stopping smoking in COPD patients are summarized in **Table 2**.

TABLE 2: Benefits of cessation in COPD smokers

> Decreased prevalence of respiratory symptoms
> Reduced number of hospitalizations
> Respiratory symptoms improve in the first year post-cessation
> Annual FEV1 decline is reduced, with a cumulated decline in 5 years of 72ml following cessation compared to 301ml in continuing smokers
> Reduction in all-cause mortality
> The most effective measure to reduce COPD progression
> Improves responses to bronchodilator drugs and to inhaled corticosteroids
> Reduces bronchial infections

Source: Jimenez Ruiz and Undermer et.al., 2014[1]

RECOMMENDATIONS:

- Smoking cessation is recommended for all COPD patients who smoke regardless of stage of disease in order to slow COPD progression, reducing exacerbation rates, increase the effectiveness of COPD treatments and overall quality of life (Level of Evidence A).
- Future research is recommended to support more benefits of smoking cessation in COPD, especially at early stages of the disease, but also in hard-core smokers with severe, oxygen dependent and poor quality of life COPD forms.

1.6 Smokers with COPD: what makes it hard to treat?

Physicians and other health care professionals who treat COPD patients must be aware of the complexity and heterogeneity of the clinical profile of the disease and of its implications for daily social and family life. It is not only a chronic obstructive pulmonary disorder, but also a systemic disorder; COPD is often associated with various co-morbidities that aggravate the condition and have a progressive and unpredictable evolution towards respiratory failure and over time, multiple therapeutic solutions are often needed to ensure survival. Most COPD patients experience depression, anxiety, and nutrition disorders, and of-

ten need to reduce their physical and sexual activity, and have limited independence in their daily routines. More severe COPD patients may develop life-threatening exacerbations, need permanent oxygen therapy, increased dosing or combined pharmacotherapy, and/or require hospitalization. The unique characteristics of COPD patients who smoke, requires a personalized approach to support cessation.

1.6.1 Disease course and co-morbidities

The dual nature of COPD is characterized by both respiratory and systemic manifestations. Destruction of lung parenchyma and systemic inflammation causes its multifaceted clinical presentations.[71]

Both respiratory (dyspnea, sputum, hypoxemia, etc.) and systemic (depression, anxiety, anemia, reduction in body mass, etc.) symptoms are typical found in COPD patients. As well, various cardiovascular, respiratory, metabolic, etc. co-morbidities may accompany COPD.[72]

Newly developed tools to assess COPD severity or health related quality of life (specific COPD questionnaires) are capable of providing a more adequate evaluation of the disease, in it's multiple dimensions. Whereas some are more adequate for clinical research, like the composite BODE (BMI, Obstruction, Dyspnea, Exercise) index,[73] or the St George's Respiratory Questionnaire (SGRQ), others, like the COPD Assessment Test (CAT) for clinical practice, may be of assistance with the rapid diagnosis of COPD status (See Figure 1). CAT is a simple 8-item test that measures the general impact of COPD on a patient's health and is recommended for use at any COPD visit (Fig.1).

Co-morbidities seem to be present in the majority of COPD patients. Studies show that up to 94% of COPD patients have at least one co-morbid disease and up to 46% have three or more.[74] As such, it seems logical to urge smoking cessation in those COPD patients who develop smoking induced co-morbidities, especially for cardiovascular disorders and lung cancer.

Non-small cell lung cancer is often associated with co-existing COPD. Smoking is a common risk factor for both diseases independently, but some authors have studied how smoking affects the risk of developing the combined disease. Studies have found that ex-smokers and smokers have a ~5–10-fold higher risk to develop the combined disease as compared to developing cancer alone. Smoking dosage was the most important risk factor for the combined disease, especially in women and among patients with a squamous cell carcinoma subtype, pointing to gender- and cancer subtype specific influences on the combined disease.[75]

FIGURE 1: COPD Assessment Test (CAT)

Name: Today's Date:

CAT™
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

Example: I am very happy 0 X 2 3 4 5 I am sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

Source: Glaxo Smith Kline 2009, http://www.catestonline.org/english/indexEN.htm

Cardiovascular co-morbidities in COPD include increased frequency of: arterial hypertension, related to the increased systemic inflammation observed in COPD, congestive heart failure and coronary heart disease. Arterial hypertension is correlated with higher Medical Research Council dyspnea scores, reduced capacity for physical activity,[76] and airflow obstruction.[77]. Atrial fibrillation is also frequently encountered in COPD patients, especially in severe forms of COPD; atrial flutter and non-sustained ventricular tachycardia, as well.[78] Hospitalization mortality in severe COPD patients with arrhythmia has been reported to be as high as 31%, compared with 8% in non-COPD patients.[79] Coronary heart disease is found in ≥30% of COPD patients, so recognizing the signs and symptoms of coronary heart disease is vital in COPD patient care.[80] Both diseases are characterized by chronic sustained inflammation and coagulopathy. The key mediator of this sustained inflammation in COPD is probably elevated C-reactive protein levels, which not only maintain bronchial constriction but also increase the risk for coronary disease.[81] Pulmonary artery hypertension and subsequent right heart failure are observed in COPD patients as a consequence of pulmonary artery remodeling, in about 40% of cases.[82] When COPD patients develop pulmonary artery hypertension, they experience more intense shortness of breath, greater desaturation during exercise, and more profound limitation of physical activity; so, they often require oxygen therapy to improve their health status.[78] Another great problem posed to clinicians in charge of COPD patients is co-existing venous thromboembolism. The prevalence of venous thromboembolism in COPD patients during an exacerbation has been reported to be as high as 29%.[83] The prevalence of pulmonary embolism in COPD patients is also documented to be higher than in non-COPD patients and increases with age.[84]

Special consideration should be given to patients with other respiratory co-morbidities, when occurring in addition to COPD and tobacco use. Patients with Asthma and COPD who smoke, would need immediate intervention to stop tobacco use, as continuing smoking would accelerate lung function decline and increase exacerbations, but also to the trinomial condition COPD-smoking-pulmonary TB, which is not rare in countries with high prevalence of tuberculosis and of tobacco use.[85] Smokers have a higher risk of being infected with tuberculosis bacilli and once infected they develop tuberculosis disease more often than non-smokers.[18] When TB is developed in a COPD smoker, who does not stop using tobacco, both his respiratory conditions will aggravate and smoking will significantly reduce the effectiveness of TB treatment.[18] In both these situations described above, smoking cessation will prove difficult to obtain and a personalized approach is recommended.

Diabetes and metabolic syndrome are other common co-morbidities, diagnosed in 18.7%,[86] respectively in 22.5%[87] of COPD subjects, as their common denominators are smoking and systemic inflammation.[88] Diabetes is shortening the time to first COPD hospitalization and increasing hospitalization time and risk of death during exacerbations,[89] it is also increasing Medical Research Council dyspnea scores, and reducing six-minute walking distance.[76]

Osteoporosis is another chronic illness that frequently coexists with COPD, even in male patients,[90] up to

69% in some reports, reflecting not only common risk factors, like age and cigarette smoking, but also the harmful effects of COPD due to systemic inflammation, reduced physical activity, and in some cases oral steroid therapy.[91] Patients with COPD and osteoporosis tend to have higher dyspnea scores[76] lower body mass index values and more severe airway obstruction.[92]

Loss of fat-free mass (cachexia) and skeletal muscle dysfunction (myopathy) are common and severe co-morbidities of COPD, the latter having as common ground smoking and systemic inflammation, oxidative stress, and physical inactivity.[93]

COPD patients, on the other hand, comprise a heterogeneous group of patients who, in addition to heavy smoking, often display a variety of addictive characteristics, such as alcohol abuse.[94-96] Smoking and drinking 15+ units/week was found to be the riskiest behavior for all causes of death.[97] No data were found on risk of alcohol and tobacco poly-addiction in COPD smokers, but clinical experience has found that among this group of patients, the most difficulty quitting smoking is described in those who are heavy drinkers. Future research on this subject is strongly recommended and a personalized approach, consequently.

Symptoms of anxiety and depression are two of the most common co-morbidities in people with COPD,[98] leading to significantly poor health outcomes, reduced quality of life and significantly increased healthcare costs.[99] It therefore seems appropriate that clinicians caring for patients with COPD should screen them for psychological distress and manage this co-morbidity appropriately.[100] In a retrospective, observational, real life study, Gratziou and colleagues reported that the prevalence of depression in COPD patients with severe airway obstruction (FEV1 <50%) was 25% and they had 2.5 times greater risk of depression than healthy smokers.[101] High prevalence of depression is independently associated with smoking[102] and failure to give it up.[103] Depression is also one of the withdrawal symptoms that predicts relapse to smoking.[104] Patients with anxiety and depression often suffer from low self-confidence or self-efficacy, which may lead to worsened disease related coping[105] and poor self-care behaviors, such as: unwillingness to engage in pulmonary rehabilitation, decreased physical activity, failure to quit smoking, poor eating habits, and poor medication adherence.[106, 107] A useful description of the consequences of anxiety for COPD clinical practice can be found in Table 3.100 New diagnostic tools and treatment options that comprehensively recognize patients' mental health and addiction profiles, and evaluate the patient's need of psychiatric help and/or medication, may prove beneficial for certain patient groups in their smoking cessation and could reduce mortality in these patient groups. In conclusion, co-existing addiction and psychiatric diseases significantly decrease the cessation success rates in COPD smokers and increase mortality among these patients.[108]

TABLE 3: Consequences of anxiety in COPD

ACUTE/UNSTABLE PHASE	STABLE PHASE
– Panic associated admissions – Hospitalization costs – Inappropriate escalation of COPD pharmacotherapy – Possible failure to accept hospitalization when needed – Reduced survival	– Poorer quality of life – Continued smoking – Poor medication compliance – May decline vaccinations – Poor inhaler technique – Avoidance of helpful interventions such as exercise, physical activity and pulmonary rehabilitation – Disruption of normal social and employment functioning

Source: Heslop-Marshall K., 2014[100]

1.6.2 Critical Categories of COPD Smokers

COPD exacerbations, in particular those requiring hospitalization and emergency care are critical situations that require immediate action in order to address smoking cessation. It is well recognized that tobacco smoking is related to greater susceptibility to respiratory infections and that continuing smoking will increase exacerbation rate in COPD patients.[18, 109] Besides common bacterial infections, COPD exacerbations may be caused also by viral agents, due to cigarette smoke that may lead to RNA or acute episodes of influenza viruses[110]

Another difficult to approach category of COPD patients are the oxygen dependent patients. It is unfortunately not uncommon for an oxygen dependent COPD patient to continue to smoke, especially in populations with lower socio-economic or educational status[85] Long-term oxygen therapy (LTOT) decreases mortality in patients with advanced COPD and chronic hypoxemia,[111] still the prognosis is poor with a mortality rate of 51% at 2 years.[112] In such critical patients, frequently described co-morbidities like congestive heart failure or pulmonary embolism and impaired gas exchanges may additionally worsen COPD prognosis, therefore continuing smoking should absolutely be excluded.[113]

Several studies have identified the association between low education and/or socio-economic status and COPD. In the Finnish elderly population, COPD has proved to be most common among those with a low socio-economic status and history of smoking and working in dusty occupations.[114] Low socio-economic status was a determinant of COPD independently of smoking.[115] In a large population-based study, further evidence was found to confirm that there was an independent association with COPD and low education.[116]

1.6.3 Pattern of tobacco use and dependence in COPD smokers

Although smoking cessation is strongly indicated by international guidelines as an effective therapeutic tool for patients with COPD, a large proportion of patients do not quit smoking and they are regarded as a "difficult" target group. For successful smoking cessation, it is important to understand the difficulties smokers are experiencing that influence their efforts to quit smoking. Health care providers should be aware of the COPD patient's pattern of smoking when approaching intervening in order to maximize the likelihood of successful quitting.

Disease severity and risks due to previous or continuing smoking should be used as arguments to motivate towards cessation. However, smoking cessation can be difficult to achieve, especially among patients with higher levels of nicotine dependence.[117, 118] Even after receiving smoking cessation support, COPD patients may not be able to quit smoking.[119] In order to understand why individuals diagnosed with COPD continue to smoke, qualitative studies are required, but very few have been published. One available study showed that having respiratory symptoms was not reason enough to quit, as many of the smokers felt alienated and unworthy of smoking cessation support as they regarded their disease as self-inflicted.[9]

As well, perception of the etiology of their disease is an important factor in the decision to quit smoking. Walters and Coleman found that patients who attribute their respiratory symptoms to smoking are 8 times (95% CI 3.0 –23.3) more likely to believe that their health will improve if they stop smoking, and 6 times (95% CI 1.4-23.3) more likely to intend to stop smoking.[40]

There is strong evidence that smokers with COPD have specific characteristics that make it hard to succeed with quitting tobacco.[1, 18] In particular, tobacco users with COPD smoke more cigarettes per day and are more highly addicted to nicotine compared to the general population of tobacco users.[54, 55] Prevalence of severe dependence, defined as a Fagerstrom Test for Nicotine Dependence (FTND) score ≥ 7, was higher in COPD subjects, by comparison to non-COPD subjects: 28.8% vs. 10.2% ($p < 0{,}0001$).55 Another study found that each additional FTND point was associated with an increase of 11% in the probability of developing COPD.[120]

Some reports indicate that COPD smokers inhale a greater volume of smoke and inhale more deeply than smokers without COPD, so, as more toxic substances reach the lungs, they will have increased levels of biomarkers of tobacco exposure.[1, 54] COPD disease pattern (depression, anxiety, etc.) is associated with a lack of motivation and self-confidence for quitting, thus reducing the odds of quitting smoking.[121] Depression is underestimated in subjects suffering from COPD. Its prevalence ranges from 6 to 46 % and it was shown to be more important in COPD smokers than in healthy smokers.[67]

Van Eerd and colleagues showed that smokers with COPD tried to quit smoking as often as smokers without COPD and were just as motivated to try again in the future, even though they utilized smoking cessation treatments more often.[122] However, despite the fact that they were more often advised by their GP to stop smoking compared to non-COPD smokers, they did not make more attempts to quit.[122]

Smokers with COPD are more likely to smoke for social reasons, to get an energy boost and as a habit; and believe that cessation treatments are more expensive than non-COPD smokers. So, it has been reported that COPD patients who smoke have a lower level of self-efficacy to refrain from smoking in emotional and habitual situations, compared to non- COPD smokers, and it is recognized that self-efficacy is an important predictor of smoking cessation.[123] A higher motivational support would help such patients.[122]

Studies about factors that predict smoking cessation are contradictory. A strong motivation to quit, adherence to the intervention protocol and using cessation pharmacotherapy seem good predictors, while sex, number of pack-years, severity of nicotine dependence and severity of airway obstruction do not seem to predict successful cessation.[67] Gorecka and colleagues showed three predictors of successful abstinence in COPD smokers: age under 55 ($p<0.001$), number of packs-years under 20 ($p<0.001$) and a FEV1 under 88% of predicted ($p<0.01$).[124] Van Schayck and colleagues believe two factors can predict abstinence at 12 months: a lower FTND score and lack of previous use of nicotine replacement therapy.[125] To achieve a successful long term smoking cessation it might be more effective to first ensure that the smoker has the right internal motivation to make the decision to quit, and then assist with smoking cessation.[126] It would be advantageous to tailor smoking cessation support to two distinct groups (unmotivated smokers and smokers motivated to quit). Advantages of quitting should be discussed with unmotivated smokers, and the smokers motivated to quit should be supported to increase their self-efficacy and action planning.[127]

In summary, smokers with COPD differ from the general population of tobacco users on several factors that are associated with tobacco smoking and quitting. Understanding these differences and tailoring cessation interventions may assist with increasing effectiveness of smoking cessation treatments among smokers with COPD.

RECOMMENDATIONS:

- All health care providers who treat COPD patients who smoke should be aware of the specific tobacco use and cessation patterns of this group of patients in order to tailor intervention strategies and increase success with quitting (Level of Evidence D).
- There is a need for more research on tailoring smoking cessation interventions in COPD patients who smoke.

2.0
EFFECTIVE SMOKING CESSATION INTERVENTIONS FOR COPD PATIENTS

The majority of COPD patients, in particular those who report high levels of nicotine dependence require structured smoking cessation programs.16 Current best practice recommends that people with COPD should be encouraged to quit smoking and provided with both non-pharmacological and pharmacological therapy to support cessation.[1, 16, 128-131]

The combination of pharmacotherapy and behavioral counselling is also the recommended approach for the general population of tobacco users.[132] This recommendation is supported by evidence generated from several systematic reviews. A 2016 systematic review by the Cochrane Collaboration of smoking cessation interventions of people who smoke with COPD found evidence that a combination of high-intensity behavioural treatment plus pharmacotherapy was superior to no treatment or to psychosocial interventions alone or compared to low intensity behavioural treatment.[131] A review of smoking cessation interventions for COPD patients by Pires-Yfantouda et. al., which covered literature published up to 2010, identified four studies. The review found psychosocial interventions combined with pharmacotherapy are effective in increasing smoking cessation at 12 months post-intervention (quit rate 35.5% in the experimental groups vs.10% in the control group), however due to small sample size the effect was not statistically significant (OR 2.35, 95% CI 0.25–21.74).[133] A 2013, review by Lira-Mandujano and colleagues which examined the efficacy of three types of tobacco treatment interventions in hospitalized patients also found the combination of pharmacological and psychological therapy was superior to no intervention, but data was limited given that only a few clinical trials have examined the effectiveness of psychological interventions in patients with COPD.[134]

RECOMMENDATIONS:

- A growing body of evidence suggests that majority of COPD patients', in particular those who report high levels of nicotine dependence will require a structured and intensive smoking cessation support in order to quit (Level of Evidence B).
- A combination of high-intensity counselling and pharmacotherapy is the most effective strategy for treating tobacco use among patients with COPD (Level of Evidence B).

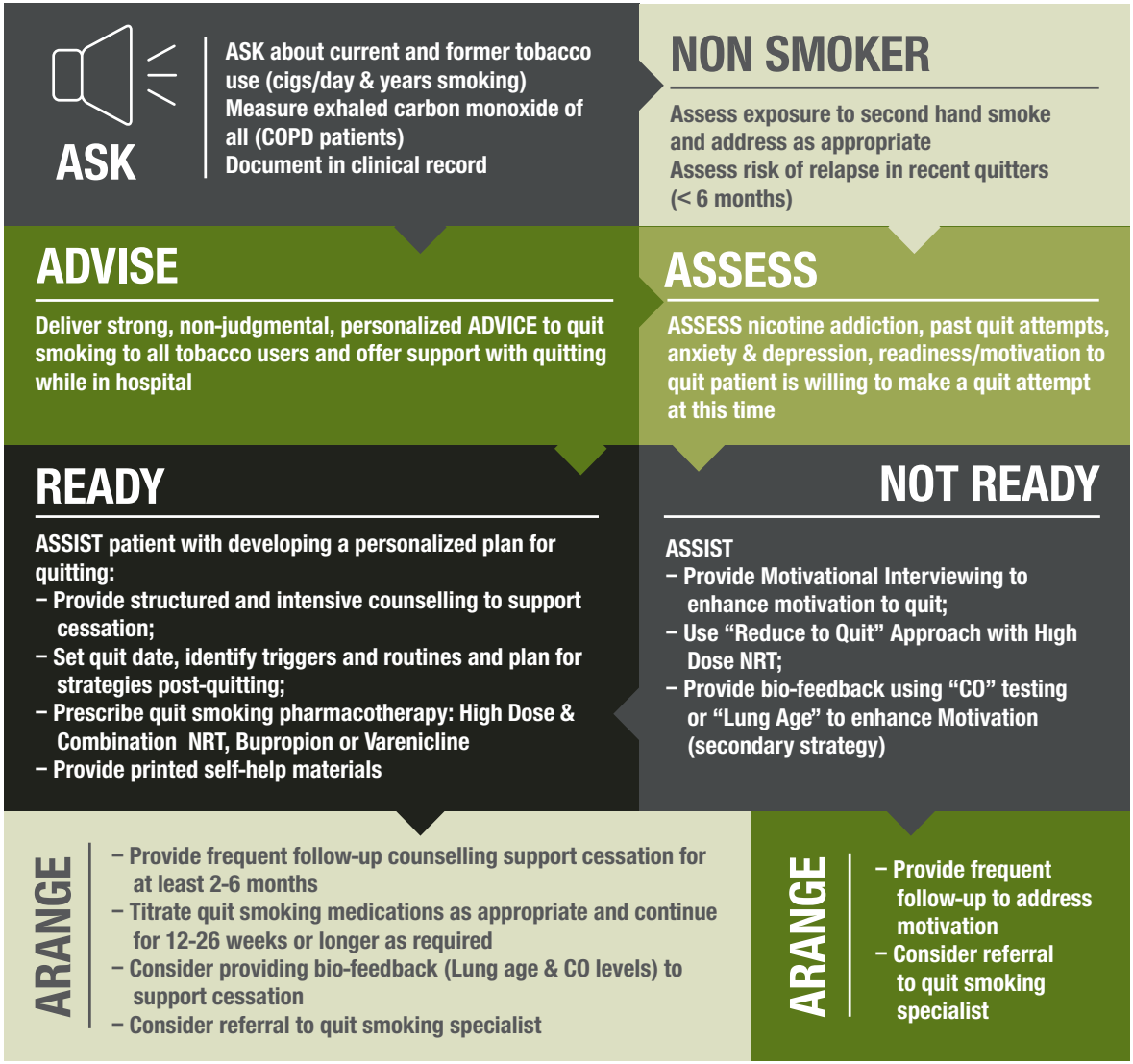
2.1 Integrating smoking assessment and cessation into routine primary and secondary care

COPD is a frequent and growing health problem in daily practice for many categories of specialists: pulmonologist, internal medicine and general practitioners, in particular. Despite persistent warnings about the importance of quitting smoking for preventing COPD development and progression, there are still many patients who continue to smoke, even years after being diagnosed with COPD. There is great need to identify the most appropriate and efficient strategies for assisting COPD patients in understanding the benefits of quitting smoking without delay and support treatment in this very high-risk population of tobacco users.

Five strategies are recommended for addressing tobacco use in clinical settings. Known as the 5As these strategies are:[12]

- **Ask** all patients about smoking status,
- **Advise** patients who smoke to quit,
- **Assess** readiness to quit,
- **Assist** with making a quit attempt, including providing behavioral counselling and prescribing first-line smoking cessation medications, and
- **Arrange** follow-up

FIGURE 2: 5As Tobacco Treatment Protocol for COPD patients



Smoking should be routinely screened in all COPD patients, by questionnaire. This should include an assessment of current tobacco use, cessation history, and tobacco dependence (e.g. Fagerstrom test for nicotine dependence- see Figure 3). The key questions of the FTND are questions 1 and 4: the number of cigarettes smoked daily and the time of the first cigarette after waking up in the morning. These questions may be asked by a doctor during consultation and constitute the short version test, scored from 0 to 6, with the same score values as the 6-item version of FTND.

FIGURE 3: Fagerström Test for Nicotine Dependence (FTND)

1. How soon after you wake up do you smoke the first cigarette?		
	Under 5 minutes	3 points
	6-30 minutes	2 points
	31-60 minutes	1 point
	More than 60 minutes	0 points
2. Does it feel difficult for you to abstain from smoking in places where smoking is banned (e.g. church, cinema, train, restaurant etc.)?		
	Yes	1 point
	No	0 points
3. Which cigarette would it be the most difficult for you to give up?		
	The first cigarette in the morning	1 point
	All the others	0 points
4. How many cigarettes/day do you smoke?		
	10 or fewer	0 points
	11-20	1 point
	21-30	2 points
	31 or more	3 points
5. Do you smoke more frequently in the first hours after you wake up than in the rest of the day?		
	Yes	1 point
	No	0 points
6. Do you smoke if you are so ill that you are immobilized in bed most of the day?		
	Yes	1 point
	No	0 points

Score 0-3: no or low tobacco dependence
Score 4-6: medium tobacco dependence
Score 7-10: high tobacco dependence

Source: Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO.The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire.vBr J Addict, 1991 Sep;86(9):1119-27)

Pulmonologists

Available information indicates that, even if the majority of pulmonologists are assessing patient smoking behavior and motivation to quit, most of them are not assisting patients with quitting as part of their practice rou-

tines.[135] In a nationwide survey conducted among Dutch pulmonologists (n=320), of whom 63% responded, the majority of respondents were not convinced that the 5As (ask, advise, assess, assist, arrange) method would result in more patients quitting, and were pessimistic about their ability to use it.[135] A study in which patients were asked to report on the smoking cessation advice provided by their primary care physician found considerably less advisory behavior by physicians than reported by the study of Bolman and colleagues.[136] Training in smoking cessation guidance skills is useful for all pulmonologists, as they already treat smokers with tobacco induced respiratory disorders. Cabana et al. showed that previous training in smoking cessation counselling was associated with higher levels of self-efficacy in assessing smoking status and counselling a patient to quit smoking afterwards.[137] A Cochrane review showed that training health professionals to provide smoking cessation interventions has measurable effects on professional performance and patients' smoking cessation behavior.[138]

RECOMMENDATIONS:

- Smoking cessation interventions should be integrated into routine care of COPD patients who smoke, in both primary care and specialist settings (Level of Evidence A).
- Primary care providers, pulmonologists and other health professionals involved in the treatment of COPD should be trained in evidence-based smoking cessation treatment and be prepared to provide smoking cessation pharmacotherapy and counselling to their COPD patients or may refer them to a colleague trained in smoking cessation (Level of Evidence A).

2.2 Non-pharmacological smoking cessation interventions

2.2.1 Behavioral Counselling

The most important non-pharmacological intervention for quitting smoking is behavioral counselling. Behavioral counselling may assist with eliminating barriers and provide personalized feedback to increase abstinence rates in patients with COPD.[134]

The 2016 ENSP Guidelines for Treatment of Tobacco Dependence identifies three categories of behavioral counselling interventions: psychological support for smoking cessation, cognitive-behavioral therapy (CBT) and motivational interviewing (MI). All three intervention approaches have common elements, to treat psychological and behavioral dependence of tobacco users.

Psychological support combines psychological education and motivational techniques with therapeutic elements. Psychological support is carried out in a systematized and standardized approach. It starts with an evaluation of the patient's psychological characteristics, and assists patients in comparatively evaluating benefits over disadvantages in a personalized manner, as well as the influence that their tobacco dependence will have

on their own life. Positive outcomes are discussed; with an emphasis on positive achievements and strong support of the patient's own self-confidence.[16]

CBT aims to change an individuals' tobacco use by changing habitual ways of thinking and feelings about smoking and oneself and provides encouragement and advice on ways of minimizing and managing the desire to smoke.[139] Through CBT the smoker will learn practical techniques for dealing with smoking-inciting situations and will benefit from psychological and behavioral support for encouraging him/her to stop smoking completely.[16]

MI is a counseling style built on improving the counselor's understanding of how to communicate and relate better to the patient. MI seeks to create a collaboration relationship between the health care professional and patient and uses 'active listening' – which refers to re-phrasing what the patient says. MI seeks to avoid an aggressive or confrontational approach and tries to steer people towards choosing to change their behavior, and to encourage their self-belief. MI means the counselor must show empathy, highlight discrepancies, avoid resistance, and support self-reliance and patient's ability to change.[140]

A variety of formats have been tested for delivering non-pharmacologic smoking cessation treatments including: individual counselling, proactive telephone counselling, group counselling, web-based, and self-help in the general population. There is no specific evidence that one delivery format is superior for COPD patients. However intensity of intervention appears to be an important factor (see below).

Bartlett and colleagues performed a meta-analysis of 17 randomized controlled trial (RCT) (n=7,446) on "effective behavior change techniques (BCT) in smoking cessation interventions for people with COPD"; the review specifically sought to identify which BCTs are associated with more effective smoking cessation interventions for people with COPD.141 The overall quit rate in the intervention group was 13.2% and the sample weighted effect size was +0.33 (95% CI 0.23 to 0.43). There was significant heterogeneity across the 17 studies in terms of the intervention design and effect sizes. Authors found four techniques were associated with significantly larger effect sizes: 1) facilitate action planning/develop treatment plan, 2) prompt self-recording, 3) advice on methods of weight control, and 4) advise on/facilitate use of social support. While assessing nicotine dependence was found to have a modest influence on intention to quit, authors recommend measuring motivation and self-regulation capacity prior to conducting the intervention, so that time and resources can be devoted to the particular issues faced by participants (forming strong intentions to quit and/or the effective implementation of quit intentions).

In a RCT, 3562 patients with COPD who were current smokers were allocated to intervention group receiving behavioral intervention and control group receiving the usual care for two years. Behavioral intervention doubled the smoking cessation rate in patients with COPD.[142] However, in a recent study by Yap and colleagues investigating the possible efficacy of adding adjunctive psychological intervention for COPD smokers accessing standard smoking cessation interventions, it was found that poor quit rates for COPD smokers were not in-

creased. In the authors' opinion, while resistance to engage with this intervention and to retain those who start are barriers to achieving abstinence, the difficulties are more likely related to the complex needs of this group of patients, who are characterized by multiple quit attempts in the past, numerous co-morbid physical and mental health problems, histories of early adverse experiences and other psychosocial issues.[143]

Intensity of Behavioral Counselling

Gratziou and colleagues have studied the effectiveness of an intensive smoking cessation program in smokers with COPD and asthma under real-life conditions. Authors concluded that it is crucial for smokers with asthma or COPD of any severity to attend an intensive smoking cessation program with regular and long-term follow-up; this will help them achieve high short and long-term abstinence rates and avoid relapses. Regular attendance with frequent follow-up visits mainly for the first three months are important and the combination of medical counselling with individual behavioral support and pharmaceutical treatment can increase abstinence rates. Doctor's optimistic approach and more motivational tools to increase the patient compliance can be helpful.[101]

Three studies have examined intensity of counselling among COPD patients. In all of three studies behavioral counselling was delivered in combination with NRT and compared to those receiving usual care. One study[144] examined the effect of intensive counselling plus NRT while the other 2 studies[119, 145] used minimal counselling plus NRT. A statistically significant difference in abstinence rates favoring the intervention groups compared with usual care (RR, 4.28; 95% CI, 3.51–5.20; $p<0.001$). In a sub-group analysis of intensity of counselling, only the study using intensive counselling plus NRT showed a significant difference in abstinence rates compared with usual care ($p<0.001$). Another small observational study reported high cessation rates among COPD patients that participated in an intensive program based on cognitive behavioral therapy, compared to asymptomatic participants. One hundred percent follow-up was achieved and biochemically-validated prolonged abstinence after one year was 42%.[146]

RECOMMENDATIONS:

- There is no convincing evidence of the effectiveness of any specific psychosocial intervention for patients with COPD due to lack of a sufficient number of high-quality studies (Level of Evidence C).
- There is growing evidence and expert opinion about the importance of intensive forms of behavioral counselling to support cessation in the population of COPD smokers (Level of Evidence C).
- Future research should assess whether the needs of patients with COPD are truly different than the needs of healthy smokers. If so, future randomized controlled trials should investigate if tailoring interventions to those needs improves quit rates in patients with COPD.

2.2.2 Use of COPD questionnaires

The Clinical COPD Questionnaire (CCQ) was developed as a valuable, 10-item tool for assessing the health-related quality-of-life gains attributable to smoking cessation among COPD patients.[147] CCQ asks patients to answer questions about symptoms, functional and mental status, during the past 7 days, on a 7 point scale, allowing for the calculation of an overall clinical COPD control score and scores of the three domains, that are calculated by adding all the scores together and dividing the sum by the number of questions (See Figure 4). By administering the CCQ in a subgroup of COPD patients, who received cessation advice ± medication to quit, 2 months post successful cessation, an increase was documented in health rated quality of life in a significant number of health domains.[148]

FIGURE. 4: CLINICAL COPD QUESTIONNAIRE

CLINICAL COPD QUESTIONNAIRE
Please circle the number of the response that best describes how you have been feeling during the past week. (Only one response for each question)

On average, during the past week, how often did you feel:	never	hardly ever	a few times	several times	many times	a great many times	almost all the time
1. Short of breath at rest?	0	1	2	3	4	5	6
2. Short of breath doing physical Activities?	0	1	2	3	4	5	6
3. Concerned about getting a cold or your breathing getting worse?	0	1	2	3	4	5	6
4. Depressed (down) because of your breathing problems?	0	1	2	3	4	5	6
In general, during the past week, how much of the time:							
5. Did you caugh?	0	1	2	3	4	5	6
6. Did you produse phlegm?	0	1	2	3	4	5	6

CLINICAL COPD QUESTIONNAIRE Please circle the number of the response that best describes how you have been feeling during the past week. (Only one response for each question)							
On average, during the past week, how limited were you in these activities because of your breathing problems:	not limited at all	very slightly limited	slightly limited	moderately limited	very limited	extremely limited	totally limited/ or unable to do
7. Strenuous physical activities (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
8. Moderate physical activities (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
9. Daily activities at home (such as dressing, washing yourself)?	0	1	2	3	4	5	6
10. Social activities (such as talking, being with children, visiting friends/ relatives)?	0	1	2	3	4	5	6

CCQ Questionnaire Scoring: CCQ Total Score = (item 1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9 + 10)/10; Symptom = (item 1 + 2 + 5 + 6)/ 4; Functional State = (item 7 + 8 + 9 +10)/4; Mental State = (item 3 + 4)/2
Source: http://www.hqlo.com/content/1/1/13

2.2.3 Spirometry and "Lung Age"

Spirometry and "Lung Age" are two simple tests that busy clinicians can use to address tobacco use and deliver more personalized advice to quit advising smokers to quit.

Lung Age, an estimate of the age at which the FEV_1 would be considered normal, was developed to present spirometry data in an understandable format and to serve as a tool to encourage smokers to quit. Many primary care physicians and pulmonary disease specialists have in their practices such, small, "pocket" devices and may use these to calculate

"lung age". "Lung age" can be used to communicate to patients the impact of tobacco use on their respiratory function. In a study investigating primary care physicians' views of using "lung age" to help COPD patients to quit smoking, most providers considered "lung age" easy to communicate. Moreover, some found the tool to be less judgmental for smoking cessation and others remarked on the merits of having a simple, tangible number to discuss with their patients, and its feasibility to use with COPD patients who smoke. Confrontation with regular spirometry tests may help demonstrate to persistent smokers (including those who do not admit their status) that their lung function is declining and help motivate patients to quit.[149] It has been suggested that the treatment for smoking cessation in smokers with COPD should include motivational interviewing and personalized feedback with the use of measures of spirometry, and of "lung age".[143] Annual spirometry with a brief smoking cessation intervention, followed by a personal letter from a doctor, had a significantly higher three-year abstinence rate among COPD smokers, compared to smokers with normal lung function.[150] In a study by Kotz and colleagues, 296 smokers with no prior diagnosis of COPD were detected with mild-to-moderate airflow limitation by means of spirometry and randomly allocated to: confrontational counselling by a nurse with nortriptyline for smoking cessation (experimental group); regular counselling by a nurse with nortriptyline (control group 1); or "care as usual" for smoking cessation by the general practitioner (control group 2). Only the experimental group was confronted with their abnormal spirometry (mean FEV_1 in one second) post-bronchodilator 80.5% of predicted mean FEV_1/forced vital capacity post-bronchodilator 62.5%). Study results did not provide evidence that the confrontational approach increases the rate of long-term abstinence from smoking compared with an equally intensive treatment in which smokers were not confronted with spirometry.[151] Further investigation in needed to explore COPD patients' perspectives of obtaining their lung age to help motivate them to quit.[152]

2.2.4 Biochemical validation of the self-reported smoking status of patients with COPD

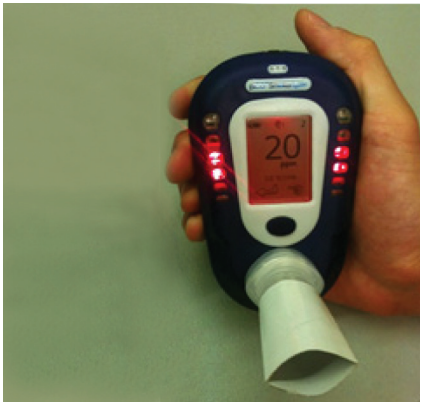
Many COPD patients do not provide a valid self-report of their smoking status and many physicians are skeptical about the accuracy of self-reports. A cross-sectional smoking-status validation study included 60 patients with COPD who reported that they had stopped smoking and found the sensitivity of the self- report of smoking was 29% and the specificity was 100%.[145] In such cases, biochemical validation of smoking status represents a useful tool and may improve outcomes of cessation interventions. Biological assessment refers to some specific biomarkers, allowing objective proof of tobacco exposure, like carbon monoxide (CO) in exhaled air, cotinine (a nicotine metabolite that can be measured in plasma, saliva, urine, hair and intranasal) but also anatabine, anabasine, thiocyanate, uric acid and nitric oxide (NO), identified by more recent research.[153]

CO can be most easily monitored and represents an indicator of sure tobacco consumption. CO concentration in a smoker's body is determined if the patient exhales in a CO analyzer. The CO unit is ppm (parts per million), a parameter that can be converted to equivalent % carboxyhemoglobin reading, by a micro smokerlyzer device (**Figure 5**).

The toxicity of CO is influenced by blood saturation, CO level in the air and breath air volume. Additional factors like environmental pollution (exhaust gas), passive smoking, professional exposure or smoke from biomass/coal burning may induce confusion in interpretation of CO values, yet active smoking remains the major cause to increase CO levels. In normal conditions, in non-smokers, exhaled CO is < 4 ppm. Careful interpretation of CO is required in some special situations, when CO levels may register higher than estimated values, such as in COPD smokers, for example. In these patients, a higher CO ratio is either explained by the production of CO as a result of the chronic airway inflammatory processes in COPD, or it is simply due to the more intense smoking described by this category of patients.[18] Jimenez Ruiz and colleagues reported higher CO levels in COPD versus non-COPD smokers: 19,7 ± 16,3 vs. 15,4 ± 12,1 ppm ($p<0.0001$).[54] The measurement of exhaled CO and NO may represent a new method for the noninvasive monitoring of airway inflammation and oxidant stress in COPD ex-smokers. Exhaled CO and NO are strongly affected by cigarette smoking, which limits their usefulness as bio-markers in current smokers.[154]

CO measurement has also been used as a tool to enhance patient motivation to quit. The fast conversion of CO to normal values encourages the smoker to be abstinent and thus demonstrates lower CO values at each follow-up visit, which supports the quitting attempt. There is however insufficient evidence to support the use of CO monitoring in comparison to standard treatment. Given its value, as a motivational tool it is recommended that specialized smoking cessation centers should be equipped with a CO analyzer. The use of CO analyzers in other settings such as primary care is also a good practice.[16]

FIGURE 5:
Expiratory carbon monoxide (CO) monitoring device (micro smokerlyzer)



Source: https://covita.net/comonitors.html

Cotinine is another biomarker for tobacco use. Cotinine is the main metabolite of nicotine and is a biomarker of exposure to tobacco smoke. By monitoring the concentration of cotinine in the body, one can assess an individual's tobacco smoke exposure. Cotinine can be measured in blood, hair, saliva and urine. The half-life of nicotine is about two hours; however nicotine concentration can vary depending on the time of the day when the last cigarette was smoked.[155] Cotinine has a half-life of 15-20 hours and as such can be used to measure 24-48 hour smoking abstinence. In smokers, plasma cotinine is about 200 ng/ml, but may reach up to 1000 ng/ml depending on the intensity of smoking.[156] There is considerable variation among individual smokers in levels of cotinine and daily intake of cigarettes.[155-157] Rates of nicotine metabolism are genetically determined and can influence cotinine levels. A cut-off of < 15 ng/ml for saliva and of 50 ng/ml for urine is recommended.[155-157] In situations where the patient is using nicotine replacement therapy, measurement of cotinine is not recommended. In these cases CO monitoring is the preferred method of validation.[156] The use of cotinine levels has not been found to be more sensitive than using clinical symptom monitoring to adapt the therapeutic dose of cessation medications.[158] As such, cotinine assessment is not at the present time recommended as a tool for guiding clinical practice.[16]

RECOMMENDATIONS:

- Exhaled air carbon monoxide (CO) and cotinine are useful non-invasive bio-markers of tobacco smoking exposure and can be used in clinical settings to assess smoking status and to monitor smoking cessation (Level of Evidence A).
- Clinicians overseeing the care of COPD smokers should take the opportunity to assess CO values whenever possible in follow-up visits and use it as a motivational tool to support quit attempts, being at the same time aware of the higher CO levels due to airway inflammatory process (Level of Evidence B).
- The role of "lung age" for increasing patient motivation to quit smoking deserves further investigation (Level of Evidence C).
- More studies are needed to identify best practices for integrating bio-chemical validation of tobacco use into smoking cessation interventions addressed to COPD smokers.

2.3 Pharmacological Interventions for Smoking Cessation in COPD Patients

Available literature shows that prescribing medication for stopping smoking is an important target for treating COPD smokers. Three first-line pharmacotherapies are recommended and have been shown to double or triple six month smoking abstinence compared to placebo: nicotine replacement therapy (NRT), varenicline and bupropion.[67] An overview of first line quit smoking medications with proven efficacy in COPD smokers is described in **Table 4**.

TABLE 4: Quit Smoking Medications with Proven Efficacy among COPD Patients

SUBSTANCE	MODE OF APPLICATION	DOSAGE	SPECIAL REMARKS
Nicotine Replacement Therapy	Patch	3 strengths (Preparations differ by manufacturer) To be used over 16 or 24 hours	– Long acting (24-hours) – May be used in combination with fast acting NRT – Possible skin reaction
	Chewing gum	2 mg, 4 mg Maximum daily dosage: 25 pieces (2 mg) or 15 pieces (4 mg)	– Problematic in patients wearing dentures – Undesirable side effects: heartburn, oral irritation
	Sublingual lozenge	2mg Maximum daily dosage 30 lozenges	– Fast acting – Undesirable side effect: oral irritation
	Lozenge	1 mg, 2 mg, 4 mg, maximum daily dosage 30 lozenges (2 mg lozenge)	– Fast Acting – Undesirable side effect: oral irritation
	Nasal spray	0.5 mg per actuation, 1 actuation Maximum dosage: twice per hour in each nostril	– Undesirable side effects: irritation of the mucosa
Varenicline	Tablet	0.5 mg 1x daily for 3 days, then 0.5 mg 2x's daily for 4 days, followed by quitting smoking, followed by 1 mg 2x's daily for 12 weeks	– Undesirable side effects: nausea, vivid dreams
Bupropion	Tablet	150 mg 1x daily for 7 days, then followed by quitting smoking, followed by 150 mg 2x's daily Total duration of treatment: 8 weeks	– Undesirable side effects: cerebral seizures nausea, sleep disturbances

Source: Andreas S, Batra A, Behr J, et al: Tabakentwöhnung bei COPD [smoking cessation in COPD]. guideline published by the German Society for Pneumology and Respiratory Medicine. Pneumologie 2008; 62: 255-72 (12). (With permission from Thieme-Verlag, Stuttgart)

2.3.1 Nicotine replacement therapy (NRT)

NRT is available in the form of a long-acting patch, and short-acting gum, inhaler, spray and lozenge. NRT has been shown to double quit rates in the general population of tobacco users and triple quit rates when two forms of NRT are used in combination.[12]

NRT is used to assist with reducing cravings and withdrawal symptoms related to quitting. NRT dosing is gradually reduced over time.

Several studies have examined the use of NRT as a quit smoking aid among COPD patients. The combination of nicotine chewing gum and intensive individual counselling for a sustained period significantly increases prolonged abstinence from smoking in patients with mild airways obstruction.[121] In an open, randomized study examining four different NRT regimens used in daily routine for COPD patients in a lung disease clinic, the average 12-month success rate for the three considered active treatments was only 5.6%.[17] In another study, Tonnesen et al. evaluated the efficacy of nicotine sublingual tablets and two levels of behavioral support for smoking cessation in COPD patients.[159] They found that abstinence rates were significantly superior in the sublingual nicotine group vs. placebo, even though there was no significant difference between the effects of low vs. high behavioral support.

An analysis of 7,372 COPD patients showed that smoking cessation counseling in combination with NRT had the greatest effect on prolonged abstinence rates versus usual care, versus SCC alone and versus SCC combined with an anti-depressant.[129] These studies found NRT to be superior to placebo; however quit rates reported are lower than in the general population of tobacco users and reflect the difficulty of supporting cessation in the COPD patient population.

A large body of evidence supports the use of higher doses of NRT in patients who report higher levels of nicotine addiction. This is particularly relevant to COPD patients who are known to have higher levels of nicotine addiction (See Table 5 for guideline regarding dosing instructions). The combination of two types of NRT with different types of delivery (i.e. long-acting patch and short-acting gum, inhaler, or spray) is highly recommended. The dosing of NRT should aim to match the daily cigarette consumption of the tobacco user, as shown in Table 5; i.e. 1mg-1.5mg of nicotine replacement therapy for each cigarette consumed per day by the patient (i.e. 20 cigarettes per day = 20-30 mg of NRT).

Increasing the length of time that NRT is used is also an evidence-based strategy for increasing success with quitting. COPD patients may require six to twelve months of NRT therapy to achieve cessation versus the standard 10-week therapy course.

NRT can be used to help in the progressive reduction of the number of cigarettes smoked as a gateway to quitting permanently. COPD smokers are usually unmotivated to quit. Using this approach can help to increase own motivation and build up self-efficacy in quitting.[160]

RECOMMENDATIONS:

- NRT can be used to support cessation among COPD patients; however standard dosing of NRT among COPD populations has produced lower quit rates than in the general population of smokers (Level of Evidence A).
- High dose NRT is recommended for patients who report moderate to high levels of nicotine addiction as measured by the Fagerstrom Test of Nicotine Dependence. The combination of two types of NRT with different types of delivery is highly recommended (Level of Evidence A).
- Increasing the length of time that NRT is used to up to six or twelve months can be effective in increasing abstinence rates compared to the standard 10 weeks of NRT therapy (Level of Evidence A).
- For COPD patients with low motivation to quit, NRT may be used to support gradual smoking reduction (Level of Evidence B).

TABLE 5: Proposed initial doses of nicotine replacement therapy

TIME TO FIRST CIGARETTE IN THE MORNING	Number of Cigarettes per day			
	<10 cigs/d	10-19 cigs/day	20-30 cig/day	> 30 cig/day
< 5 mins		Patch High Dose (0.9 mg/h) +/- oral NRT	Patch High Dose (0.9 mg/h) +/- oral NRT	2 High Dose Patches (1.8 mg/h) +/- oral NRT
< 30 mins		Patch High Dose (0.9 mg/h)	Patch High Dose (0.9 mg/h) +/- oral NRT	Patch High Dose (0.9 mg/h) +/- oral NRT
< 60 mins after waking	No medication or oral NRT	Oral NRT	Patch High Dose (0.9 mg/h)	Patch High Dose (0.9 mg/h) +/- oral NRT
> 60 mins after waking	No medication or oral NRT	No medication or oral NRT	Oral NRT	
Non-daily	No medication or oral NRT	No medication or oral NRT		

Source: European Network for Smoking and Tobacco Prevention (ENSP). Guidelines for Treating Tobacco Dependence, 2nd Edition. Brussels, Belgium; 2016.[16]

2.3.2 Bupropion

Bupropion is a non-nicotine therapy for smoking cessation available in tablet form, by prescription only. Bupropion has been found to mimic the effect of cigarette-derived nicotine by inhibiting the re-uptake of noradrenaline and dopamine and is thought to reduce nicotine withdrawal also by this mechanism.[161] It seems that bupropion's efficacy for nicotine dependence is distinct from its anti-depressant action, since its positive smoking cessation action has also been proven on non-depressive patients.[162]

In three clinical trials that analyzed the efficacy of bupropion for treatment of smokers with COPD, it was found that bupropion was significantly more effective than placebo for achieving continuous abstinence at six-month follow-up (16% v. 9%),[163] that bupropion was more effective than placebo for achieving continuous abstinence at six-month follow-up (27.9% v. 14.6%).[164] Bupropion combined with counselling was significantly more effective in achieving prolonged abstinence than a placebo by 18.9% (95% CI 3.6-26.4%).[164]

RECOMMENDATIONS:

- Bupropion is an effective aid to support smoking cessation among COPD patients and it is safe to use bupropion in this population of tobacco users (Level of Evidence B).

2.3.3 Varenicline

Varenicline is a partial agonist of the α4β2 nicotinic acetylcholine receptor, offering a two-pronged approach to treating the addiction: as a partial agonist of the nicotinic receptor, this drug reduces the symptoms and signs of nicotine withdrawal, while it simultaneously blocks some of its reinforcing effects.[165] Varenicline produces approximately 50 percent of the receptor stimulation provided by nicotine, and blocks the effects of any nicotine taken in from cigarette smoking.

The efficacy and safety of varenicline for treating COPD smokers was evaluated in two studies: a multi-centre, double-blind study (n=504) of patients with mild to moderate COPD and without known psychiatric disorders and another open label study of 472 smokers with severe or very severe COPD who received treatment for smoking cessation. In the first study, the continuous abstinence rate for weeks 9 to 12 was significantly higher for patients in the varenicline group (42.3%) than for those in the placebo group (8.8%), respectively and 18.6% vs. 5.6% through weeks 9 to 52.[166] In the second study, as the treatment programme consisted of a combination of behavioral therapy and drug treatment (NRT, bupropion or varenicline), the continuous abstinence rate from 9 to 24 weeks for NRT, bupropion and varenicline was 38.2%, 60.0% and 61.0%, respectively.[167]

RECOMMENDATIONS:

- Varenicline is a first-line quit smoking medication that has been shown to be effective in supporting cessation in smokers with COPD, regardless of disease severity or number of cigarettes smoked (Level of Evidence B).

2.3.4 Nortriptyline

One study reported abstinence rates in patients with COPD receiving minimal counselling plus nortriptyline compared with those receiving usual care.[151] No significant difference in abstinence rates was found between the intervention group and the usual care group (RR 1.91; 95% CI 0.65–5.61; p=0.24). Although the study itself was of high quality, patients enrolled into this study had undiagnosed COPD and were only classified by the GOLD criteria upon entering the study. Since patients were unaware of their COPD diagnosis, they may not have been as motivated to quit smoking or to take their illness as seriously as patients who had been previously diagnosed with COPD.

RECOMMENDATIONS:

- There is limited evidence to recommend the use of nortriptyline for smoking cessation in COPD patients (Level of Evidence C).

2.3.5 Minimal Counselling and combination use of NRT and Bupropion versus Usual Care

The efficacy of receiving minimal counselling, NRT, and a prescribed antidepressant (bupropion) compared to usual care was examined in one study.[145] The study was conducted in an outpatient setting. There was no statistically significant difference in abstinence rates between the intervention and usual care arms (RR, 2.25; 95% CI, 0.87–5.85; P = 0.10). Although the study itself was of high quality, several factors may have contributed to the lack of success of the intervention including: the inclusion of some unmotivated COPD smokers, less intensive counselling (the intervention was integrated into routine care), and poor compliance with the use of bupropion and NRT noted at follow-up.[145]

2.4 Cost-effectiveness of Smoking Cessation in COPD

Various tools are in use to estimate cost-effectiveness in COPD: health outcomes are expressed as life-years (LY) and quality-adjusted life-years (QALY). In the particular situation of COPD, many aspects must be considered,

such as: transition to higher severity GOLD stage, COPD exacerbation rates, adding other tobacco related co-morbidities, costs of usual versus acute care, etc. Analysis of cost-effectiveness of therapies for quitting smoking in COPD patients can provide future landmarks for best practices for assisting this high-risk group.

In an evidence-based analysis to determine the effectiveness and cost-effectiveness of the smoking cessation interventions in the management of COPD, Thabane and the Ontario COPD Working Group, 2012, provided a useful resource for ranking the effectiveness of cessation interventions in COPD.[130] This analysis revealed abstinence rates statistically higher in those receiving intensive counseling compared to usual care (RR, 7.70; 95% CI, 4.64–12.79; P <0.00001),[145, 168] a significant difference in abstinence rates compared with usual care (P < 0.001) for intensive counseling + NRT144 and a statistically significant difference in abstinence rates when using NRT versus placebo (P=0.05)159 but also in patients with COPD receiving an antidepressant in a placebo-controlled trial (P<0.001).[164]

Sicras-Mainar and colleagues performed research on a retrospective cohort nested case-control study of male and female COPD outpatients, 40 years or older, covered by a health provider and a health plan. Cases were current smokers with COPD and controls (two per case), former smokers with COPD (at least 12 months without smoking), matched for age, sex, duration of COPD, and burden of co-morbidity. They found that current smokers with COPD had significantly higher use of healthcare resources, mainly for COPD medication and for physician visits, compared with former smokers who had abstained for at least 12 months. As a consequence, current smokers had higher healthcare costs to the National Health System in Spain than ex-smokers.[169]

In a simulation model for smoking cessation cost-effectiveness, Atsou and colleagues estimated the specific burden of continuous smoking, as well as the effectiveness and the cost-effectiveness of smoking cessation. Their study offered a useful support for the setting of smoking cessation programs specifically targeted to COPD patients.[170]

In a systematic review of RCTs, Hoogendoorn and colleagues analyzed the long-term effectiveness and cost-effectiveness of smoking cessation interventions in COPD, and concluded that 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.[128] Compared with intensive counselling, pharmacotherapy was cost saving and dominated the other interventions. The authors analyzed the effectiveness of continued assistance in smokers with COPD, concluding that despite the high costs for this aggressive smoking cessation program, beneficial economic effects are likely to be obtained in the long run.[128]

In a research paper published in 2016, Cadier and colleagues performed a cost-effectiveness analysis based on 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, in current French smokers aged 15–75 years. Their results were expressed by "the incremental cost-effectiveness ratio in 2009 Euros per life year gained (LYG) at the lifetime horizon". Authors found potential cost savings for lung cancer, COPD and cardiovascular disease rang-

ing from €15 million to €215 million at the five-year horizon for an initial cessation treatment cost of €125 million to €421 million. They concluded that "providing medical support to smokers in their attempts to quit is very cost-effective and may even result in cost savings".[171]

3.0
SETTING SPECIFIC SMOKING CESSATION INTERVENTIONS FOR COPD PATIENTS

Various setting-specific interventions to approach smoking cessation for COPD patients are described below, except primary care interventions, which have been summarized in section 2.1.

3.1 Pharmacist-led interventions

COPD patients must visit periodically their pharmacist for COPD regular or exacerbation related prescriptions. Such opportunities could be utilized to provide quit smoking advice. A survey published in 2012 by Verma and colleagues explored the degree to which community pharmacists in North West England identify and provide advice to smokers and assess prescribed inhaled corticosteroids to COPD patients. Questionnaires were sent to 2080 community pharmacists from the 2005 pharmacist census database. Of the 1051 respondents, 37.1% mentioned smoking as a COPD risk factor most or every time and 54.5% sometimes or rarely. 19.6% routinely asked about smoking status when dispensing COPD medication. Pharmacists with more than 20 years' experience were more likely to have read the guideline compared to pharmacists with 10 years or less (OR: 1.54; 95% CI: 1.13 to 2.10). Pharmacists who have read the NICE Guideline (46.8%) were around twice as likely to mention smoking as a risk factor for COPD, to ask about COPD if inhaled corticosteroids were dispensed and to ask about smoking routinely if COPD medication was dispensed. ($p<0.005$). Authors concluded that the NICE guidelines on COPD encourage community pharmacists to carry out smok-

ing cessation and educational interventions, but further support is needed.[172]

3.2 Nurse-led Interventions

A RCT evaluated the effectiveness of brief advice alone or accompanied by individual nurse support or group support facilitated by nurses. Smoking status was biochemically validated and stage of change, nicotine addiction and dyspnea were recorded at 2, 3, 6, 9 and 12 months. After 12 months, cessation rates were not significantly different between groups (p=0.7), but all groups had a significant reduction in their nicotine addiction (p=0.03–0.006). No changes in subjects' motivation or dyspnea were detected over the 12 months. There is a need to develop and test specific nurse-led interventions for use in patient populations with respiratory conditions.[119]

3.3 Smoking cessation for hospitalized patients

Three studies examined the efficacy of smoking cessation counselling versus usual care in patients with COPD in an inpatient setting. One study145 included an intervention of intensive counselling (defined as ≥ 90 minutes), while the other study168 compared minimal counselling (defined as < 90 minutes) to that of usual care. Abstinence rates were statistically higher in those receiving intensive counselling compared to usual care (RR, 7.70; 95% CI, 4.64–12.79; P <0.00001). Sundblad and colleagues investigated abstinence outcomes after 1 and 3 years, in a group of COPD patients who participated in a 1-year smoking cessation program, compared with those of a group of COPD patients who received usual care.[173] The smoking cessation program included a 2-week period of hospitalization. Nicotine replacement therapy and physical exercise were recommended, and education was given in group sessions. Feedback and encouraging comments by phone from the specially trained staff continued during the full year. Follow-ups were performed 1 and 3 years after the start of the smoking cessation program. This comprehensive smoking cessation program with hospitalization and a long follow-up period resulted in high quit rates even after 3 years. Despite high costs for this aggressive smoking cessation program, beneficial economic effects seemed likely to be obtained in the long run.[173]

In a recently published study, Meltzer and colleagues investigated whether pharmacological treatment for stopping smoking dispensed to patients hospitalized for COPD was associated or not to 6-12 months smoking abstinence. Based on review of medical records, authors found that among 33.7 % of patients receiving cessation pharmacotherapy in the next 90 days post hospital discharge, 19.8% reported they have quit smoking at 6-12 months, and concluded such key interventions could bring substantial benefits in COPD smokers.[174]

3.4 Smoking cessation for respiratory out patients

A 2015 study examined the feasibility and potential effectiveness of an adapted version of the Ottawa Model for Smoking Cessation (OMSC) in an out-patient respirology clinic.[175] The OMSC is a clinical approach to tobacco dependence treatment found to increase smoking abstinence by an absolute 11% of hospitalized patients.[176] Implemented in more than 300 Canadian health care sites, the OMSC incorporates the '5As' approach to consultation (Ask, Advise, Assess, Assist and Arrange), pharmacotherapy and follow-up support though an automated telephone triage system to link smokers requiring assistance to nurse specialist counselling. In a small pilot, randomized control study comparing an adaptation of the OMSC intervention group to standard care, the intervention group received a brief counselling in clinic which included discussion regarding: the pros/cons of smoking, potential challenges to quitting, smoking triggers and encouragement, a voucher for $110 towards the purchase of four to five weeks' worth of pharmacotherapy (nicotine replacement therapy [NRT], bupropion, varenicline) and telephone-based follow-up support. The control group received the standard smoking cessation treatment including strong physician advice, and an information brochure on smoking cessation aids and a prescription for pharmacotherapy if requested. The quit rate for intervention participants was 18.2% vs. 7.7% for controls (OR 2.36; 95% CI 0.39 to 14.15). Authors found that: alternatives to face-to-face clinic visits were preferred, a comparable number of subjects in both groups chose to take pharmacotherapy and that financial incentive was useful in completion of smoking status CO validation.[175] Such pilot interventions could serve as a model to tailor smoking cessation interventions for COPD outpatients.

3.5 Rehabilitation programs for COPD patients

Specific treatment for COPD consists of both pharmacological and non-pharmacological methods interventions, such as pulmonary rehabilitation (PR) and self-management (SM) programs. Pulmonary rehabilitation, including patient education, exercise training, psychosocial support and nutritional intervention complement pharmacological therapy,[177] while self-management programs ('individual's ability to manage symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition) have been promoted for helping people with chronic conditions. In a review of 51 RCTs, Sohanpol and colleagues found high study participation rates and low dropout rates in research studies of PR, SM and health education (HE) programs and strongly endorsed the active implementation of PR and SM programs in routine care as patients with COPD are participating, attending and completing them.[178] Smoking cessation should be integrated in rehabilitation programs for COPD patients.

3.6. Family-focused smoking cessation interventions for COPD patients

In a systematic review, to assess the effectiveness of family-focused smoking cessation interventions for people with COPD, Luker and colleagues were unable to find sufficient evidence.[179] The term "family" was used inclusively for those people identified in the literature as family members or significant others. The findings from this review clearly indicated that the family and social environment of the patient is infrequently considered in smoking cessation interventions for people with COPD.[179] Only one study[180] was identified which considered the family context when designing the smoking cessation intervention (purposely situating the intervention in the participant's home) and, even in this study, there was no report of actually how or if the family was involved in the intervention. Further research is recommended to determine if a more family-focused intervention, in conjunction with pharmacological and counselling approaches, would lead to improved smoking cessation outcomes.[179]

RECOMMENDATIONS:

- Smoking cessation should be integrated into inpatient treatment of COPD and rehabilitation programs for COPD patients (Level of Evidence C).
- Further research is needed to explore various combination interventions, in various settings and format delivery, to address smoking cessation in COPD patients.

1. Jiménez-Ruiz CA, Andreas S, Lewis KE, et al. Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. Eur Respir J. 2015.
2. Global Initiative for chronic obstructive lung disease (GOLD). Guidelines: global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2007.
3. Jeffery P. K. Remodeling and inflammation of bronchi in asthma and chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2004;1(3):176-83.
4. Murray C. J., Lopez. A.D. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997;349(9064):1498-504.
5. Vernooy JH, Küçükaycan M, Jacobs JA, et al. Local and systemic inflammation in patients with chronic obstructive pulmonary disease: soluble tumor necrosis factor receptors are increased in sputum. Am J Respir Crit Care Med. 2002;166(9):1218-24.
6. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370(9589):165-73.
7. U.S. Department of Health E, and Welfare,. 28 Surgeon General's Reports on Smoking and Health, 1964–2004 2004.
8. Ward B. www.smokehaz.eu – a review of the evidence on smoking and lung health. Eur Respir J. 2014.
9. Wilson JS, Elborn JS, D. F. 'It's not worth stopping now': why do smokers with chronic obstructive pulmonary disease continue to smoke? A qualitative study. J Clin Nurs 2011;20:819-27.
10. Nizet TA, van den Elshout FJ, Heijdra YF, van de Ven MJ, Mulder PG, Folgering HT. Survival of chronic hypercapnic COPD patients is predicted by smoking habits, comorbidity, and hypoxemia. Chest. 2005;127(6):1904-10.
11. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Guidelines: global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2015.
12. Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: US Dept of Health and Human Services, Public Health Service; 2008.
13. West R, McNeill A, Raw A. Smoking cessation guidelines for health professionals: an update. Thorax. 2000;55(12):987-99.
14. Ministry of Health. The New Zealand Guidelines for Helping People to Stop Smoking. Wellington: Ministry of Health. 2014.
15. Ontario Health Technology Advisory Committee. OHTAC Recommendation: Chronic Obstructive Pulmonary Disease

REFERENCES

(COPD). 2012.

16. European Network for Smoking and Tobacco Prevention (ENSP). Guidelines for Treating Tobacco Dependence, 2nd Edition. Brussels, Belgium; 2017.
17. Tønnesen P, Carrozzi L, Fagerström KO, et al. Smoking cessation in patients with respiratory diseases: a high priority, integral component of therapy. Eur Respir J. 2007;29(2):390-417.
18. European Network for Smoking and Tobacco Prevention aisbl (ENSP). European Smoking Cessation Guidelines: The authoritative guide to a comprehensive understanding of the implications and implementation of treatments and strategies to treat tobacco dependence. First Edition; 2012.
19. de Marco R, Accordini S, Marcon A, et al. Risk factors for chronic obstructive pulmonary disease in a European cohort of young adults. Am J Respir Crit Care Med. 2011;183(7):891-7.
20. de Marco R, Accordini S, Antò JM, et al. Long-term outcomes in mild/moderate chronic obstructive pulmonary disease in the European community respiratory health survey. Am J Respir Crit Care Med. 2009;180(10):956-63.
21. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1(6077):1645-8.
22. García Rodríguez LA, Wallander MA, Tolosa LB, Johansson S. Chronic obstructive pulmonary disease in UK primary care: incidence and risk factors. COPD. 2009;6(5):369-79.
23. Lundbäck B, Lindberg A, Lindström M, et al. Not 15 but 50% of smokers develop COPD?--Report from the Obstructive Lung Disease in Northern Sweden Studies. Respir Med. 2003;97(2):115-22.
24. Marsh S, Aldington S, Shirtcliffe P, Weatherall M, Beasley R. Smoking and COPD: what really are the risks? Eur Respir J 2006;28:883-6.
25. Sherrill DL, Lebowitz MD, Knudson RJ, Burrows B. Smoking and symptom effects on the curves of lung function growth and decline. Am Rev Respir Dis 1991;144(1):17-22.
26. Anthonisen NR, Skeans MA, Wise RA, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142(4):233-9.
27. Retamales I, Elliott WM, Meshi B, et al. Amplification of inflammation in emphysema and its association with latent adenoviral infection. Am J Respir Crit Care Med 2001;164(3):463-73.
28. Shapiro SD. The macrophage in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;160(5 Pt 2):S29-32.
29. Finkelstein R, Fraser RS, Ghezzo H, Cosio MG. Alveolar inflammation and its relation

to emphysema in smokers. Am J Respir Crit Care Med. 1995;152(5 Pt 1):1666-72.
30. Lacoste JY, Bousquet J, Chanez P, et al. Eosinophilic and neutrophilic inflammation in asthma, chronic bronchitis, and chronic obstructive pulmonary disease. J Allergy Clin Immunol. 1993;92(4):537-48.
31. Casolaro MA, Bernaudin JF, Saltini C, Ferrans VJ, Crystal RG. Accumulation of Langerhans' cells on the epithelial surface of the lower respiratory tract in normal subjects in association with cigarette smoking. Am Rev Respir Dis. 1988;137(2):406-11.
32. Soler P, Moreau A, Basset F, Hance AJ. Cigarette smoking-induced changes in the number and differentiated state of pulmonary dendritic cells/Langerhans cells. Am Rev Respir Dis 1989;139(5):1112-7.
33. O'Shaughnessy TC, Ansari TW, Barnes NC, Jeffery PK. Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of CD8+T lymphocytes with FEV1. Am J Respir Crit Care Med. 1997;155(3):852-7.
34. Shapiro SD, Goldstein NM, Houghton AM, Kobayashi DK, Kelley D, Belaaouaj A. Neutrophil elastase contributes to cigarette smoke-induced emphysema in mice. Am J Pathol 2003;163(6):2329-35.
35. Shapiro SD, Senior RM. Matrix metalloproteinases. Matrix degradation and more. Am J Respir Cell Mol Biol. 1999;20(6):1100-2.
36. Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. Tob Control. 2003;12(4):424-30.
37. Tuder RM, Petrache I. Pathogenesis of chronic obstructive pulmonary disease. J Clin Invest. 2012;122(8):2749-55.
38. Talhout R, Schulz T, Florek E, van Benthem J, et al. Hazardous compounds in tobacco smoke. Int J Environ Res Public Health 2011;2(8):613–28.
39. de Marco R, Accordini S, Cerveri I, et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. Am J Respir Crit Care Med. 2007;175(1):32-9.
40. Walters N, T. C. Comparison of the smoking behaviour and attitudes of smokers who attribute respiratory symptoms to smoking with those who do not. Br J Gen Pract. 2002;52(475):132-4.
41. EPA California. Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. Sacramento, CA; 2005.
42. Johannessen A, Bakke PS, Hardie JA, Eagan TM. Association of exposure to environmental tobacco smoke in childhood with chronic obstructive pulmonary disease and respiratory symptoms in adults. Respirology. 2012;17(3):499-505.
43. Jordan RE1, Cheng KK, Miller MR, Adab

REFERENCES

P. Passive smoking and chronic obstructive pulmonary disease: cross-sectional analysis of data from the Health Survey for England. BMJ Open. 2011;1(2):e000153.

44. Eisner MD, Iribarren C, Yelin EH, et al. The impact of SHS exposure on health status and exacerbations among patients with COPD. Int J Chron Obstruct Pulmon Dis. 2009;4:169-76.
45. Kim WJ, Song JS, Park DW, et al. The effects of secondhand smoke on chronic obstructive pulmonary disease in nonsmoking Korean adults. Korean J Intern Med. 2014;29(5):613-9.
46. Calverley PM, Walker P. Chronic obstructive pulmonary disease. Lancet. 2003;362(9389):1053-61.
47. Chapman KR, Mannino DM, Soriano JB, et al. Epidemiology and costs of chronic obstructive pulmonary disease. Eur Respir J. 2006;27(1):188-207.
48. Florescu A, Ferrence R, Einarson T, Selby P, Soldin O, Koren G. Methods for quantification of exposure to cigarette smoking and environmental tobacco smoke: focus on developmental toxicology. Ther Drug Monit. 2009;31(1):14-30.
49. World Health Organization (WHO). WHO REPORT ON THE GLOBAL TOBACCO EPIDEMIC, 2008 The MPOWER package. 2008.
50. Waatevik M, Skorge TD, Omenaas E, Bakke PS, Gulsvik A, Johannessen A. Increased prevalence of chronic obstructive pulmonary disease in a general population. Respir Med. 2013;107(7):1037-45.
51. Baron KP. To smoke or not to smoke: Predictors of smoking behavior in people with head and neck cancer and chronic obstructive pulmonary disease. Dissertation Abstracts International: Section B: The Sciences and Engineering, . 2003;64(2-B):954.
52. Vozoris NT, Stanbrook MB. Smoking prevalence, behaviours, and cessation among individuals with COPD or asthma. Respir Med. 2011;105(3):477-84.
53. Tønnesen P. Smoking cessation and COPD. Eur Respir Rev 2013;22(127):37-43.
54. Jiménez-Ruiz CA, Masa F, Miravitlles M, et al. Smoking characteristics: differences in attitudes and dependence between healthy smokers and smokers with COPD. Chest. 2001;119(5):1365-70.
55. Shahab L, Jarvis MJ, Britton J, West R. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. Thorax. 2006;61(12):1043-7.
56. Knuiman MW, James AL, Divitini ML, Ryan G, Bartholomew HC, Musk AW. Lung function, respiratory symptoms, and mortality: results from the Busselton Health Study. Ann Epidemiol. 1999;9(5):297-306.
57. Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the

United States: data from the First National Health and Nutrition Examination Survey follow up study. Thorax. 2003;58(5):388-93.
58. Lindberg A, Jonsson AC, Rönmark E, Lundgren R, Larsson LG, Lundbäck B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest. 2005;127(5):1544-52.
59. Lokke A, Lange P, Scharling H, Fabricius P, Vestbo J. Developing COPD: a 25 year follow up study of the general population. Thorax. 2006;61(11):935-9.
60. Hersh CP, DeMeo DL, Al-Ansari E, et al. Predictors of survival in severe, early onset COPD. Chest. 2004;126(5):1443-51.
61. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176(6):532-55.
62. Kanner RE, Connett JE, Williams DE, Buist AS. Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: the Lung Health Study. Am J Med. 1999;106(4):410-6.
63. Makris D, Scherpereel A, Copin MC, et al. Fatal interstitial lung disease associated with oral erlotinib therapy for lung cancer. BMC Cancer 2007;150(7):1-4.
64. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS. Smoking Cessation and Lung Function in Mild-to-Moderate Chronic obstructive Pulmonary Disease. The Lung Health Study. . Am J Respir Crit Care Med. 2000;161(2):381-90.
65. Laniado-Laborín R. Smoking and Chronic Obstructive Pulmonary Disease (COPD). Parallel Epidemics of the 21st Century. Int J Environ Res Public Health. 2009;6(1):209-24.
66. Godtfredsen NS, Lam TH, Hansel TT, et al. COPD-related morbidity and mortality after smoking cessation: status of the evidence. Eur Respir J. 2008;34(4):844-53.
67. Underner M, Perriot J, Peiffer G. Sevrage tabagique du fumeur atteint de bronchopneumopathie chronique obstructive. Rev Mal Respir. 2014;31(10):937—60.
68. Barnett M. COPD: Smoking cessation Community Nursing Journal. 2008;22(11):36-40.
69. van Schayck OC, Haughney J, Aubier M, et al. Do asthmatic smokers benefit as much as non-smokers on budesonide/formoterol maintenance and reliever therapy? Results of an open label study. Respir Med. 2012;106(2):189-96.
70. Beck GJ, Doyle CA, Schachter EN. Smoking and lung function. Am Rev Respir Dis. 1981;123(2):149-55.
71. Bracke KR, D'hulst AI, Maes T, et al. Cigarette smoke-induced pulmonary inflammation and emphysema are attenuated in CCR6-deficient

REFERENCES

mice. J Immunol. 2006;177(7):4350-9.

72. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. 2011.
73. Celli BR1, Cote CG, Lareau SC, Meek PM. Predictors of Survival in COPD: more than just the FEV1. Respir Med. 2008;102(Suppl 1):S27-35.
74. Sharafkhaneh A, Petersen NJ, Yu HJ, Dalal AA, Johnson ML, Hanania NA. Burden of COPD in a government health care system: a retrospective observational study using data from the US Veterans Affairs population. Int J Chron Obstruct Pulmon Dis. 2010;5:125-32.
75. Zhai R, Yu X, Wei Y, Su L, Christiani DC. Smoking and smoking cessation in relation to the development of co-existing non-small cell lung cancer with chronic obstructive pulmonary disease. Int J Cancer. 2014;134(4):961-70.
76. Schonhofer B, Wenzel M, Geibel M, Köhler D. Blood transfu¬sion and lung function in chronically anemic patients with severe chronic obstructive pulmonary disease. Crit Care Med. 1998;26(11):1824–8.
77. Miller J, Edwards LD, Agustí A, et al. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. Respir Med. 2013;107(9):1376-84.
78. Hillas G, Perlikos F, Tsiligianni I, Tzanakis N. Managing comorbidities in COPD. Int J Chron Obstruct Pulmon Dis. 2015;10:95-109.
79. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213-20.
80. Rutten FH, Vonken EJ, Cramer MJ, et al. Cardiovascular magnetic resonance imaging to identify left-sided chronic heart failure in stable patients with chronic obstructive pulmonary disease. Am Heart J. 2008;156(3):506-12.
81. Brekke PH, Omland T, Smith P, Søyseth V. Underdiagnosis of myocardial infarction in COPD - Cardiac Infarction Injury Score (CIIS) in patients hospitalised for COPD exacerbation. Respir Med. 2008;102(9):1243-7.
82. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. Eur Respir J. 2008;32(5):1371-85.
83. Tillie-Leblond I, Marquette CH, Perez T SA, Zanetti C, Tonnel AB, Remy-Jardin M. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. Ann Intern Med. 2006;144(6):390-6.
84. Gunen H, Gulbas G, In E, Yetkin O, Hacievliyagil SS. Venous thromboemboli and exacerbations of COPD. Eur Respir J. 2010;35(6):1243-8.

85. Trofor A. La tuberculose chez le fumeur: une double maladie, un patient plus difficile. Al XXI-lea Congres SRP 2014 Sibiu; 2014
86. Crisafulli E, Costi S, Luppi F, et al. Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. Thorax. 2008;63(6):487-92.
87. Cazzola M, Bettoncelli G, Sessa E, Cricelli C, Biscione G. Prevalence of comorbidities in patients with chronic obstructive pulmonary disease. Respiration. 2010;80(2):112-9.
88. Ehrlich SF, Quesenberry CP Jr, Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. Diabetes Care. 2010;33(1):55-60.
89. Baker EH, Janaway CH, Philips BJ, et al. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax. 2006;61(4):284-9.
90. Parappil A, Depczynski B, Collett P, Marks GB. Effect of comorbid diabetes on length of stay and risk of death in patients admitted with acute exacerbations of COPD. Respirology. 2010;15(6):918-22.
91. Ferguson GT, Calverley PM, Anderson JA, et al. Prevalence and progression of osteoporosis in patients with COPD: results from the TOwards a Revolution in COPD Health study. Chest. 2009;136(6):1456-65.
92. Maggi S, Siviero P, Gonnelli S, et al. Osteoporosis risk in patients with chronic obstructive pulmonary disease: the EOLO study. J Clin Densitom. 2009;12(3):345–52.
93. Seymour JM, Spruit MA, Hopkinson NS, et al. The prevalence of quadriceps weakness in COPD and the relationship with disease severity. Eur Respir J. 2010;36(1):81-8.
94. Leeman RF, McKee SA, Toll BA, et al. Risk factors for treatment failure in smokers: relationship to alcohol use and to lifetime history of an alcohol use disorder. Nicotine Tob Res. 2008;10(12):1793-809.
95. Trofor A, Mihăescu R. Smoking with alcohol use: a dangerous co-dependence. Pneumologia. 2005;54(4):203-6.
96. Ziedonis D, Hitsman B, Beckham JC, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. Nicotine Tob Res. 2008;10(12):1691-715.
97. Hart CL, Davey Smith G, Gruer L, Watt GC. The combined effect of smoking tobacco and drinking alcohol on cause-specific mortality: a 30 year cohort study. BMC Public Health. 2010;10:789.
98. Maurer J, Rebbapragada V, Borson S, et al. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Chest. 2008;134(4 Suppl):43S-56S.
99. Naylor C, Parsonage M, McDaid D, Knapp M,

REFERENCES

Fossey M , Galea A. Long-term conditions and mental health The cost of co-morbidities. The King's Fund and Centre for Mental Health 2012.

100. Heslop-Marshall K, Anthony De Soyza A. Are We Missing Anxiety in People with Chronic Obstructive Pulmonary Disease (COPD)? Ann Depress Anxiety. 2014;1(5).
101. Gratziou Ch, Florou A, Ischaki E, et al. Smoking cessation effectiveness in smokers with COPD and asthma under real life conditions. Respir Med. 2014;108(4):577-83.
102. John U, Meyer C, Rumpf HJ, Hapke U. Smoking, nicotine dependence and psychiatric comorbidity--a population-based study including smoking cessation after three years. Drug and alcohol dependence. 2004;76(3):287-95.
103. Covey LS, Bomback A, Yan GW. History of depression and smoking cessation: a rejoinder. Nicotine Tob Res. 2006;8(2):315-9.
104. Smith SS, Jorenby DE, Leischow SJ, et al. Targeting smokers at increased risk for relapse: treating women and those with a history of depression. Nicotine Tob Res. 2003;5(1):99-109.
105. Yohannes AM, Baldwin RC, Connolly MJ. Prevalence of depression and anxiety symptoms in elderly patients admitted in post-acute intermediate care. Int J Geriatr Psychiatry. 2008;23(11):1141-7.
106. Burgess A, Kunik ME, Stanley MA. Chronic obstructive pulmonary disease: assessing and treating psychological issues in patients with COPD. Geriatrics. 2005;60(12):18-21.
107. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160(14):2101-7.
108. Kupiainen H, Kinnula VL, Lindqvist A, et al. Successful Smoking Cessation in COPD: Association with Comorbidities and Mortality. Pulmonary Medicine. 2012;2012.
109. Trofor A. Infectiile respiratorii la fumatori-manifestari specifice si indicatii terapeutice. Respiro. 2002;8:9-12.
110. Tuder RM, Yun JH. It takes two to tango: cigarette smoke partners with viruses to promote emphysema. J Clin Invest. 2008;118(8):2689-93.
111. Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. . Lancet. 1981;1(8222):681-6.
112. Crockett AJ, Cranston JM, Moss JR, Alpers JH. Survival on long-term oxygen therapy in chronic airflow limitation: from evidence to outcomes in the routine clinical setting. Intern Med J 2001;31:448-54.
113. Ahmadi Z, Bornefalk-Hermansson A, Franklin KA, Midgren B, Ekström MP. Hypo-

and hypercapnia predict mortality in oxygen-dependent chronic obstructive pulmonary disease: a population-based prospective study. Respir Res. 2014;15:30.
114. Isoaho R, Puolijoki H, Huhti E, Kivelä SL, Laippala P, Tala E. Prevalence of chronic obstructive pulmonary disease in elderly Finns. Respir Med. 1994;88(8):571-80.
115. Hedberg A, Rössner S. Body weight characteristics of subjects on asthma medication. Int J Obes Relat Metab Disord. 2000;24(9):1217-25.
116. Kanervisto M, Vasankari T, Laitinen T, Heliövaara M, Jousilahti P, Saarelainen S. Low socioeconomic status is associated with chronic obstructive airway diseases. Respir Med. 2011;105(8):1140-6.
117. Davila EP, Zhao W, Byrne M, et al. Correlates of smoking quit attempts: Florida Tobacco Callback Survey, 2007. Tob Induc Dis. 2009;5:10.
118. Fagerstrom KO, Kunze M, Schoberberger R, et al. Nicotine dependence versus smoking prevalence: comparisons among countries and categories of smokers. Tob Control. 1996;5(1):52-6.
119. Wilson JS, Fitzsimons D, Bradbury I, Stuart Elborn J. Does additional support by nurses enhance the effect of a brief smoking cessation intervention in people with moderate to severe chronic obstructive pulmonary disease? A randomised controlled trial. Int J Nurs Stud. 2008;45(4):508-17.
120. Jiménez-Ruiz C, Miravitlles M, Sobradillo V, et al. Can cumulative tobacco consumption, FTND score, and carbon monoxide concentration in expired air be predictors of chronic obstructive pulmonary disease? Nicotine Tob Res. 2004;6(4):649-53.
121. Wagena EJ, Arrindell WA, Wouters EF, van Schayck CP. Are patients with COPD psychologically distressed? Eur Respir J. 2005;26(2):242-8.
122. van Eerd EA, van Rossem CR, Spigt MG, Wesseling G, van Schayck OC, D. K. Do we need tailored smoking cessation interventions for smokers with COPD? A comparative study of smokers with and without COPD regarding factors associated with tobacco smoking. Respiration. 2015;90(3):211-9.
123. Devins GM, Edwards PJ. Self efficacy and smoking reduction in COPD. Behav Ther. 1988;26c:127-35.
124. Górecka D, Bednarek M, Nowiński A, Puścińska E, Goljan-Geremek A, Zieliński J. Diagnosis of airflow limitation combined with smoking cessation advice increases stop-smoking rate. Chest. 2003;123(6):1916-23.
125. Van Schayck CP, Kaper J, Wagena EJ, Wouters EF, Severens JL. The cost-effectiveness of antidepressants for smoking cessation in chronic obstructive pulmonary disease (COPD) patients. Addiction. 2009;104(12):2110-7.

REFERENCES

126. Eklund BM, Nilsson S, Hedman L, Lindberg I. Why do smokers diagnosed with COPD not quit smoking? - a qualitative study. Tob Induc Dis. 2012;10(1):17.
127. Hilberink SR. Smoking cessation support for COPD patients in general practice. Nijmegen, Holland: Radbound University; 2013.
128. Hoogendoorn M, Feenstra TL, Hoogenveen RT, MPMH R-vM. Long-term effectiveness and cost-effectiveness of smoking cessation interventions in patients with COPD. Thorax. 2010;65:711-8.
129. Strassmann R, Bausch B, Spaar A, Kleijnen J, Braendli O, Puhan MA. Smoking cessation interventions in COPD: a network meta-analysis of randomised trials. Eur Respir J. 2009;34(3):634-40.
130. Thabane M, COPD Working Group. Smoking Cessation for Patients With Chronic Obstructive Pulmonary Disease (COPD). An Evidence-Based Analysis. Ont Health Technol Assess Ser. 2012;12(4):1-50.
131. van der Meer RM, Wagena EJ, Ostelo RW, Jacobs JE, van Schayck CP. Smoking cessation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2003(2):CD002999.
132. Stead LF, Koilpillai P, Lancaster T. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev. 2015(10):CD009670.
133. Pires-Yfantouda R, Absalom G, Clemens F. Smoking cessation interventions for COPD: a review of the literature. Respir Care. 2013;58(11):1955-62.
134. Lira-Mandujano J, Míguez-Varela MC, Sara E, Cruz-Morales SE. Psychological Approaches to Increase Tobacco Abstinence in Patients with Chronic Obstructive Pulmonary Disease: A Review. Respiratory Disease and Infection - A New Insight: InTech; 2013.
135. Bolman C, Sino C, Hekking P, van Keimpema A, van Meerbeeck J. Willingness of pulmonologists to guide COPD patients in smoking cessation. Patient Educ Couns. 2005;57(1):126-33.
136. Kava T, Taylor J, Gamble E, Partridge MR. The availability of smoking cessation advice from health professionals--a census from one East London District. Respir Med. 2000;94(10):983-4.
137. Cabana MD, Rand C, Slish K, Nan B, Davis MM, Clark N. Pediatrician self-efficacy for counseling parents of asthmatic children to quit smoking. Pediatrics. 2004;113(1 Pt 1):78-81.
138. Carson KV, Verbiest ME, Crone MR, et al. Training health professionals in smoking cessation. Cochrane Database Syst Rev. 2012;5:CD000214.
139. Spanou C, Simpson SA, Hood K, et al. Preventing disease through opportunistic, rapid engagement by primary care teams

using behaviour change counselling (PREEMPT): protocol for a general practice-based cluster randomised trial. BMC Fam Pract. 2010;11:69.
140. Miller WR, Rollnick S. Motivational Interviewing: Preparing People for Change, 2nd Edition. New York, NY: Guilford Press.; 2002.
141. Bartlett YK, Sheeran P, Hawley MS. Effective behaviour change techniques in smoking cessation interventions for people with chronic obstructive pulmonary disease: a meta-analysis. Br J Health Psychol. 2014;19(1):181-203.
142. Lou P, Zhu Y, Chen P, et al. Supporting smoking cessation in chronic obstructive pulmonary disease with behavioral intervention: a randomized controlled trial. BMC Fam Pract. 2013;14:91.
143. Yap SY, Lunn S, Pang E, Croft C, Stern M. A psychological intervention for smoking cessation delivered as treatment for smokers with chronic obstructive pulmonary disease: Multiple needs of a complex group and recommendations for novel service development. Chron Respir Dis. 2015;12(3):230-7.
144. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA. 1994;272(19):1497-505.
145. Hilberink SR, Jacobs JE, Breteler MH, de Vries H, Grol RP. General practice counseling for patients with chronic obstructive pulmonary disease to quit smoking: impact after 1 year of two complex interventions. Patient Educ Couns. 2011;83(1):120-4.
146. Willemse B, Lesman-Leegte I, Timens W, Postma D, ten Hacken N. High cessation rates of cigarette smoking in subjects with and without COPD. Chest. 2005;128(5):3685-7.
147. van der Molen T, Willemse B WM, Schokker S, ten Hacken NHT, Postma DS, Juniper E. Development, validity and responsiveness of the Clinical COPD Questionnaire. Health Qual Life Outcomes. 2003;1:13.
148. Papadopoulos G, Vardavas CI, Limperi M, Linardis A, Georgoudis G, Behrakis P. Smoking cessation can improve quality of life among COPD patients: Validation of the clinical COPD questionnaire into Greek. BMC Pulmonary Medicine. 2011;11:13.
149. Coronini-Cronberg S, Heffernan C, Robinson M. Effective smoking cessation interventions for COPD patients: a review of the evidence. JRSM Short Rep. 2011;2(10):78.
150. Stratelis G, Mölstad S, Jakobsson P, Zetterström O. The impact of repeated spirometry and smoking cessation advice on smokers with mild COPD. Scand J Prim Health Care. 2006;24(3):133-9.
151. Kotz D, Wesseling G, Huibers MJ, van Schayck OC. Efficacy of confronting smokers with

REFERENCES

airflow limitation for smoking cessation. Eur Respir J. 2009;33(4):754-62.

152. Parker DR, Eltinge S, Rafferty C, Eaton CB, Clarke JG, Goldman RE. Primary care providers' views on using lung age as an aid to smoking cessation counseling for patients with chronic obstructive pulmonary disease. Lung. 2015;193(3):321-7.
153. Lisko JG, Stanfill SB, Duncan BW, Watson CH. Application of GC-MS/MS for the analysis of tobacco alkaloids in cigarette filler and various tobacco species. Anal Chem. 2013;85(6):3380-4.
154. Montuschi P, Kharitonov SA, Barnes PJ. Exhaled carbon monoxide and nitric oxide in COPD. Chest. 2001;120(2):496-501.
155. Benowitz NL. Biochemical verification of tobacco use and cessation. Nicotine Tob Res. 2002;4:149-59.
156. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction. 2005;100(3):299-303.
157. Jarvis M J, Primatesta P, Erens B, Feyerabend C, Bryant A. Measuring nicotine intake in population surveys: comparability of saliva cotinine and plasma cotinine estimates. Nicotine Tob Res. 2003;5:349–55.
158. Berlin I, Jacob N, Coudert M, Perriot J, Schultz L, Rodon N. Adjustment of nicotine replacement therapies according to saliva cotinine concentration: the ADONIS* trial - a randomized study in smokers with medical comorbidities. Addiction. 2011;106(4):833-43.
159. Tønnesen P, Mikkelsen K, Bremann L. Nurse-conducted smoking cessation in patients with COPD using nicotine sublingual tablets and behavioral support. Chest. 2006;130(2):334-42.
160. Jimenez Ruiz CA, Cicero Guerrero AM, Mayayo Ulibarri ML, Cristobal Fernandez MI, Gonzalez GL. Phenotypic features in COPD smokers attending a smoking cessation unit. Eur Respir J. 2011;38:1562.
161. Trofor A, Mihaltan F, Pop M, Todea D, Mihaicuta S. Romanian Society of Pulmonologists Guideline for Smoking Cessation and Smokers' assistance. Tehnopres Publishing House, Iasi. 2010.
162. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2014;1:CD000031.
163. Tashkin D, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. Lancet. 2001;357(9268):1571-5.
164. Wagena EJ, Knipschild PG, Huibers MJ, Wouters EF, van Schayck CP. Efficacy of bupropion and nortriptyline for smoking cessation among people at risk for or with chronic obstructive pulmonary disease. Arch Intern Med. 2005;165(19):2286-92.

165. Stefanatou A. Smoking Cessation in Cardiovascular Patients. Hellenic J Cardiol 2008;49(6):422-31.
166. Tashkin DP, Rennard S, Hays JT, Ma W, Lawrence D, Lee TC. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. Chest. 2011;139(3):591-9.
167. Jiménez-Ruiz CA, Ramos Pinedo A, Cicero Guerrero A, Lopez Gonzalez G. Characterisitics of COPD smokers and effectiveness and safety of smoking cessation medications. Nicotine Tob Res. 2012;14(9):1035-9.
168. Pederson LL, Wanklin JM, Lefcoe NM. The effects of counseling on smoking cessation among patients hospitalized with chronic obstructive pulmonary disease: a randomized clinical trial. Int J Addict. 1991;26(1):107-19.
169. Sicras-Mainar A, Rejas-Gutiérrez J, Navarro-Artieda R, Ibáñez-Nolla J. The effect of quitting smoking on costs and healthcare utilization in patients with chronic obstructive pulmonary disease: a comparison of current smokers versus ex-smokers in routine clinical practice. Lung. 2014;192(4):505-18.
170. Atsou K, Chouaid C, Hejblum G. Simulation-based estimates of effectiveness and cost-effectiveness of smoking cessation in patients with chronic obstructive pulmonary disease. PLoS One. 2011;6(9):e24870.
171. Cadier B, Durand-Zaleski I, Thomas D, Chevreul K. Cost Effectiveness of Free Access to Smoking Cessation Treatment in France Considering the Economic Burden of Smoking-Related Diseases. PLoS ONE. 2016;11(2):e0148750.
172. Verma A, Harrison A, Torun P, Vestbo J, Edwards R, Thornton J. Are pharmacists reducing COPD'S impact through smoking cessation and assessing inhaled steroid use? Respir Med. 2012;106(2):230-4.
173. Sundblad BM, Larsson K, Nathell L. High rate of smoking abstinence in COPD patients: Smoking cessation by hospitalization. Nicotine Tob Res. 2008;10(5):883-90.
174. Melzer AC, Feemster LC, Collins MP, Au DH. Utilization and effectiveness of pharmacotherapy for Tobacco use following admission for exacerbation of COP. J Hosp Med. 2016;11(4):257-63.
175. Pakhale S, Baron J, Armstrong MA, et al. A pilot randomized controlled trial of smoking cessation in an outpatient respirology clinic. Can Respir J. 2015;22(2):91-6.
176. Reid RD, Mullen KA, Slovinec D'Angelo ME, et al. Smoking cessation for hospitalized smokers: an evaluation of the "Ottawa Model". Nicotine Tob Res. 2010;12(1):11-8.
177. Labrecque M, Rabhi K, Laurin C, et al. Can a self-management education program for patients with chronic obstructive pulmonary disease improve quality of life? Can Respir J. 2011;18(5):e77-81.

REFERENCES

178. Sohanpal R, Hooper R, Hames R, Priebe S, Taylor S. Reporting participation rates in studies of non-pharmacological interventions for patients with chronic obstructive pulmonary disease: a systematic review. Syst Rev. 2012;1:66.
179. Luker KA, Chalmers KI, Caress A-L, Salmon MP. Smoking cessation interventions in chronic obstructive pulmonary disease and the role of the family: a systematic literature review. J Adv Nurs. 2007;59(6):559–68.
180. Monninkhof E, van der Valk P, van der Palen J, et al. The effect of a minimal contact smoking cessation programme in out-patients with chronic obstructive pulmonary disease: a pre-post-test study. Patient Educ Couns. 2004;52(3):231-6. ■

5.

SMOKING CESSATION IN PATIENTS WITH CARDIOVASCULAR DISEASE

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About this Guideline

This special chapter of the European Tobacco Treatment Guideline is intended to summarize evidence regarding the health risks associated with tobacco use in patients with cardiovascular disease as well as effective approaches to supporting cessation in this important population of tobacco users.

Within the chapter clinical practice recommendations are presented for health care professionals working with cardiovascular patients. The GRADE evidence grading system has been used to rate the quality of evidence supporting each of the recommendations. The evidence grading scale reflects the type, quality and quantity of available evidence supporting the guideline recommendation. GRADE uses 4 evidence grading categories: 'high', 'moderate', 'low', 'very low' (see table below). The level of evidence grading appears in brackets at the end of each recommendation statement.

GRADE - Evidence Grading Categories:

CODE	QUALITY OF EVIDENCE	DEFINITION
A	**High**	– Further research is very unlikely to change our confidence in the estimate of effect. – Several high-quality studies with consistent results. – In special cases: one large, high-quality multi-center trial
B	**Moderate**	– Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. – One high-quality study. – Several studies with some limitations.
C	**Low**	– Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. – One or more studies with severe limitations.
D	**Very Low**	– Any estimate of effect is very uncertain. – Expert opinion. – No direct research evidence. – One or more studies with very severe limitations.

EXECUTIVE SUMMARY

SMOKING CESSATION IN PATIENTS WITH CARDIOVASCULAR DISEASE

Cardiovascular Health Effects of Tobacco Use

- Smoking is responsible for 50% of all avoidable deaths among smokers, and half of these are caused by cardiovascular disease (CVD).
- Tobacco use is a major contributor to the occurrence and development of hypertension, coronary heart disease, acute myocardial infarction, sudden cardiac death, heart failure and their complications.
- Persons exposed to second hand smoke have a 20 to 30-percent increase in risk of morbidity and mortality caused by coronary heart disease.
- Smoke-free legislation is associated with reduced incidence of myocardial infarction and mortality in the population.
- Health Benefits of Smoking Cessation
- Smoking cessation after myocardial infarction reduces cardiovascular mortality by 36-46%.
- Smoking cessation should be a priority for the primary and secondary prevention of all forms of cardiac disease and should be treated with the same rigor as other major risk factors such as diabetes, hypertension, and dyslipidemia
- Quitting smoking results in greater reductions in CVD mortality than any other secondary prevention measure, including the use of β-blockers, angiotensin-converting enzyme inhibitors, statins or aspirin. Moreover, the benefits of antihypertensive or lipid lowering drugs are significantly reduced in those who continue to smoke.
- Smoking Cessation Interventions for Patients with CVD
- The combination of pharmacotherapy and behavioral support produces greater efficacy than either alone and is recommended for all CVD patients who smoke. Behavioral interventions are most effective in promoting abstinence if they are of sufficient intensity and duration.
- Nicotine replacement therapy, bupropion and varenicline are first line quit smoking medications and have

been shown to significantly increase smoking abstinence in patients with CVD. These medications are safe to use in patents with stable CVD. Emerging evidence also supports their use in patients with acute cardiovascular disease however more research is required in this patient population.

- Hospitalization for cardiovascular disease offers an opportunity to initiate smoking cessation. In this setting, brief bedside counseling followed by telephone counseling or other follow-up after discharge has been shown to significantly increase smoking cessation rates. Starting pharmacotherapy during hospitalization increases cessation rates after discharge.
- Given the central role that smoking plays in increasing blood pressure, inducing atherosclerosis and dramatically increasing the risk of myocardial infarction, stroke, and peripheral vascular disease, smoking cessation should be seen as a fundamental responsibility of every cardiovascular specialist.

Summary of Key Recommendations for Health Professionals:

- Smoking is a major modifiable risk factor for cardiovascular diseases and should be treated with the same importance as other cardiovascular risk factors such as hypertension, dyslipidemia or diabetes (Level of Evidence A).
- Exposure to second hand smoke is nearly as dangerous as active tobacco use, as such exposure to second-hand smoke should be limited (Level of Evidence B).
- Smoke-free legislation has been associated with population-level reductions in MI events and CVD mortality and should be a priority for every country (Level of Evidence C).
- Smoking cessation is a powerful strategy for the primary and secondary prevention of cardiovascular disease and should be a clinical priority for all CVD patients who smoke (Level of Evidence A).
- Health care professionals working with CVD patients should receive appropriate training and be prepared to intervene with patients who smoke using evidence-based treatment approaches (Level of Evidence A).
- The combination of pharmacotherapy and behavioral support produces greater efficacy than either alone and is recommended for all CVD patients who smoke (Level of Evidence A).
- Behavioral interventions are effective in promoting abstinence provided they are of sufficient intensity and duration (Level of Evidence A).
- Among patients hospitalized with a CVD-related illness, smoking cessation interventions including pharmacotherapy should be initiated during hospitalization as a standard of care (Level of Evidence A). At least one month of supportive post-discharge contact will further increase rates of cessation (Level of Evidence A).
- The "5As" (ask, advise, assess, assist, arrange) model for smoking cessation should be used with CVD patients in all clinical settings (Level of Evidence A).

- Nicotine replacement therapy (Level of Evidence A), bupropion (Level of Evidence A) and varenicline (Level of Evidence A) are first line quit smoking medications and have been shown to significantly increase smoking abstinence in patients with CVD and are safe to use in patents with stable CVD.
- While there is no evidence to suggest safety concerns with the use of NRT among patients with acute coronary syndromes patients additional research is required to increase the strength of this evidence (Level of Evidence D).

TOBACCO TREATMENT PROTOCOL – CVD PATIENTS: *HOSPITAL SETTINGS* –

ASK

Document smoking status of all CVD patients upon admission

NON SMOKER

Assess exposure to second hand smoke and address as appropriate
Assess risk of relapse in recent quitters (< 6 months)

ADVISE

Deliver strong, non-judgmental, personalized ADVICE to quit smoking to all tobacco users and offer support with quitting while in hospital

Nicotine addiction, past quit attempts, readiness / motivation to quit patient is willing to make a quit attempt at this time

ASSESS

READY

ASSIST patient with developing a personalized plan for quitting
- Provide practical counselling to support cessation
- Prescribe pharmacotherapy (High Dose & Combination NRT during hospital stay, and/or Bupropion, Varenicline to support longer term abstinence)
- Provide printed self-help materials

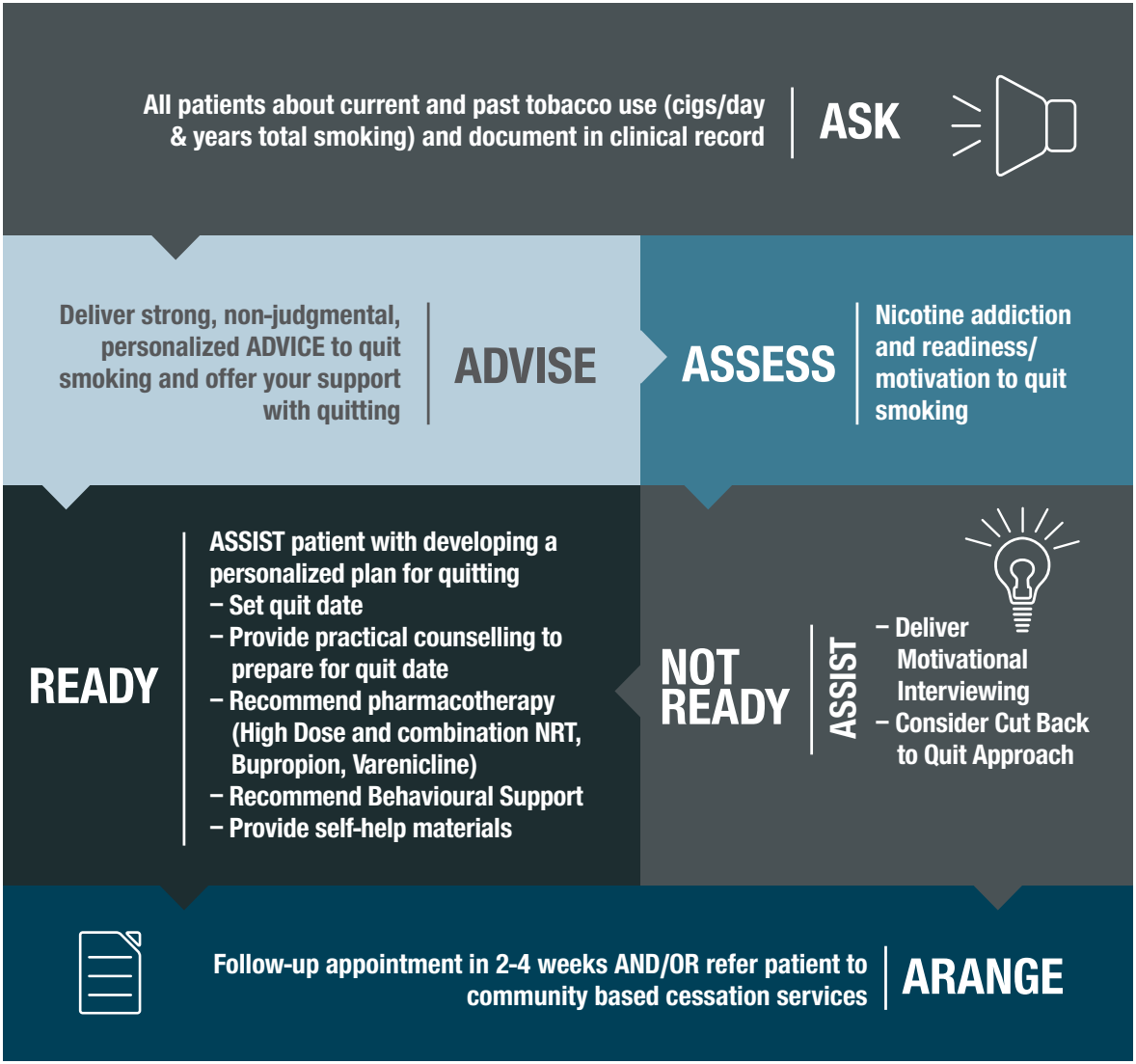
NOT READY

ASSIST with maintaining abstinence while in hospital
- Deliver brief bedside counselling to address motivation (Motivational Interviewing)
- Prescribe pharmacotherapy

- Provide follow-up councelling support while in hospital
- Titrate quit smoking medications as appropriate

ARANGE

Follow-up support (telephone-based or in-person) for at least 1-month post-discharge from hospital to support cessation


All patients about current and past tobacco use (cigs/day & years total smoking) and document in clinical record
ASK
Deliver strong, non-judgmental, personalized ADVICE to quit smoking and offer your support with quitting
ADVISE
ASSESS
Nicotine addiction and readiness/ motivation to quit smoking
READY
ASSIST patient with developing a personalized plan for quitting
– Set quit date
– Provide practical counselling to prepare for quit date
– Recommend pharmacotherapy (High Dose and combination NRT, Bupropion, Varenicline)
– Recommend Behavioural Support
– Provide self-help materials
NOT READY
ASSIST
– Deliver Motivational Interviewing
– Consider Cut Back to Quit Approach
Follow-up appointment in 2-4 weeks AND/OR refer patient to community based cessation services
ARANGE

1.0
TOBACCO USE AND CARDIOVASCULAR DISEASES

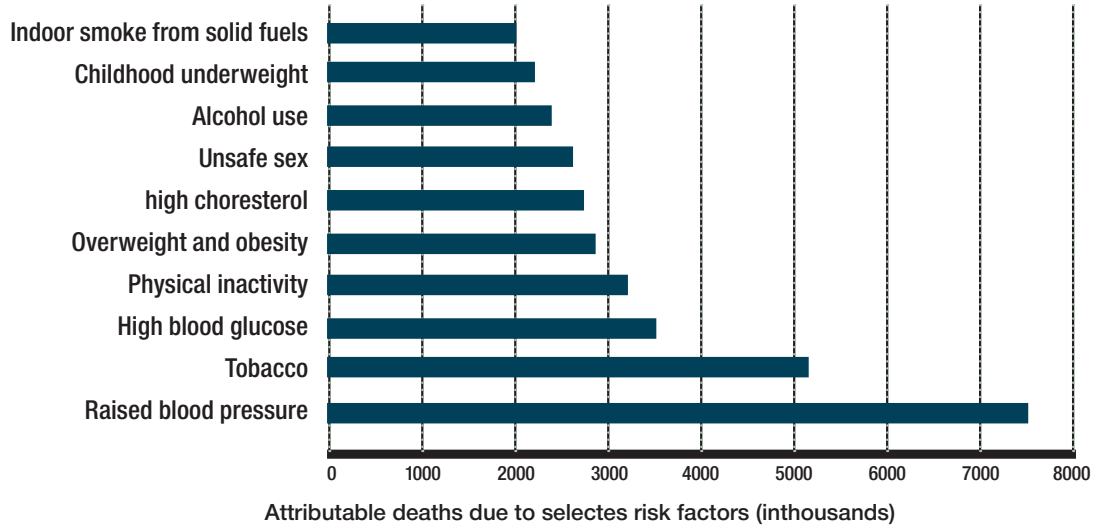
1.1 Burden of CVD and Tobacco Use

Atherosclerotic cardiovascular disease (CVD) is a chronic inflammatory disorder which results in narrowed or blocked blood vessels which can lead to chest pain (angina), heart attack or stroke.1 CVD develops throughout an individual's lifespan, usually progressing to an advanced stage by the time symptoms occur.[2]

CVDs are the leading causes of morbidity and mortality worldwide, responsible for more than 17 million deaths per year, representing 31% of all-cause mortality.[3] Almost 80% of these deaths occur in low- and middle-income countries.[4] While the age-adjusted CVD death rates have steadily declined in recent decades in developed countries, they have increased in developing countries where population density is greatest.[5] It is estimated that global mortality due to CVDs will rise to 23.6 million by 2030.[6-8] CVD is also the leading cause of premature death and disability in Europe, although CVD mortality has fallen considerably over recent decades in many European countries.[9]

Tobacco use is the second leading cause of premature death, after high blood pressure (See Figure 1).[1] Tobacco use is responsible for 50% of all avoidable deaths among tobacco users, and half of these are due to CVD.[10] Tobacco use is estimated to be responsible for 10% of all CVD cases worldwide. The cardiovascular-mortality caused by tobacco use in the population aged less than 45 years exceeds the mortality produced by any other risk factor.[11]

FIGURE 1: Attributable deaths due to selected risk factors (in thousands)



Source: Figure entitled " Attributable deaths due to selected risk factors (in thousands). From: Global atlas on cardiovascular disease prevention and control.
Page: 19 Figure: 29 - ISBN 978 92 4 156437 3 - http://apps.who.int/iris/handle/10665/4470112

1.2 Smoking as major modifiable cardiovascular risk factor

Tobacco use is a major modifiable CVD risk factor. The relationship between smoking and CVD is well documented, there is an abundance of epidemiological and clinical evidence that links cigarette smoking to the development of hypertension, myocardial infarction (AMI), coronary heart disease (CHD), peripheral vascular disease, heart failure, ischemic stroke, and sudden cardiac death.[13-19]

Cardiovascular risk refers to the likelihood of a person developing an atherosclerotic event over a defined time period.[2] Tobacco users have an increased CVD risk compared to non-smokers according to many global epidemiological studies, such as: the INTERHEART study,[20] the WHO MONICA (multinational monitoring of trends and determinants in CVD)[21] and the International Studies of Infarct Survival (ISIS).[22] The risk of coronary heart disease and cerebrovascular stroke is increased two to four fold among current tobacco users.[23] Studies have shown that smoking is strongly related to AMI[24-26] and cardiac death[27] in the general population.

The INTERHEART study, a large international case-controlled study, documented a clear dose-response relationship between smoking and the risk of AMI.[20] Yusuf et al also found that irrespective of the device used for tobacco smoking (filtered or non-filtered cigarettes, bidis [a popular South Asian cigarette], pipes or cigars), all had similar risks for AMI.[20]

Studies have also proven the association of tobacco use with hypercholesterolemia[28], with an increased reactivity of the coronaries[29] to platelet aggregation, and with a prothrombotic state[31]. Tobacco use has multiplicative effects with other risk factors associated with ischemic heart disease. Epidemiological evidence provided by Burns found that smoking increased the risk of developing ischemic heart disease twofold, while in combination with other risk factors (dyslipidemia, hypertension and diabetes), the risk of ischemic heart disease was compounded exponentially, so that a combination of any three risk factors would increase the development of ischemic heart disease eightfold.[11, 32] Moreover, the cardiovascular risk for patients with coronary disease who continue to smoke remains significantly increased even under medical therapy. There is evidence that the benefits of antihypertensive or lipid lowering drugs are significantly reduced in those who continue to smoke[33-35,] thus continuing to maintain a high cardiovascular risk in spite of medication.

There is a dose response effect between amount and duration of tobacco use and CVD risk. In a large ethnically diverse cohort McEvoy found current-smokers in the highest quartile of pack-years (number of cigarettes per day multiplied by the total number of years of smoking) of cumulative smoke exposure demonstrated increased risk for events compared with those in the lowest quartile, confirming a cumulative dose effect.[36] However, there is evidence of the harmful effects of smoking even at relatively low levels: smokers of one to five cigarettes per day experienced a 40% increase in AMI risk compared with nonsmokers, whereas those who smoked six to 10 cigarettes per day had a twofold increase in risk, and those who smoked 20 cigarettes per day had a fourfold increase in risk of heart disease.[20, 37] A review by Shane concluded that the dose response relationship between tobacco use exposure and CVD risk is non-linear and that light and intermittent smokers carry nearly the same CVD risk as daily smokers.[37]

RECOMMENDATIONS:

- Smoking is a major modifiable risk factor for cardiovascular diseases and should be treated with the same importance as other cardiovascular risk factors such as hypertension, dyslipidemia or diabetes (Level of Evidence A).
- There is no safe level of tobacco use and as such complete cessation should be the target (Level of Evidence B).

1.3 Pathogenic pathways linking smoking to cardiovascular diseases

The endothelial dysfunction and inflammation induced by smoking promote atherosclerotic plaque and thrombus formation, thus increasing the risk of hypertension, ischemic heart disease, stroke and peripheral vascular disease.[38] The compounds from cigarettes that deemed most responsible for causing CVD and stroke are nicotine, carbon monoxide and oxidant gases.[39]

Nicotine inhaled via smoking is readily absorbed via the pulmonary route and is the primary addictive agent in tobacco. Smokers may be viewed as intra-arterial drug users. Nicotine is delivered to the brain within 10-20 seconds of inhalation, with a slow decrease in arterial concentrations of nicotine between puffs.[40] The first puff brings a peak of arterial nicotine concentration of approximately 7 ng/ml, with a range of nicotine concentration in arterial blood after smoking a cigarette between 20 and 60 ng/ml.[40-42] The high rate of delivery of nicotine offered by smoking (similar to intravenous injection), leads to high levels of nicotine in the central nervous system, with short periods of use required for development of tolerance.[43] Nicotine stimulates the autonomic ganglia and the central nervous system, thus increasing the activity of the sympathetic nervous system. The release of catecholamines elevates heart rate, blood pressure and myocardial contractility, thus increasing the myocardial oxygen demand. On the other hand, the increased release of catecholamines produces coronary vasoconstriction, which reduces the myocardial oxygen supply[32]. Other associated effects of nicotine are the release of endogenous opioids and glucocorticoids[39]. The rewarding effects of nicotine are associated with nicotine receptor stimulation which leads to substantial release of dopamine and other neurotransmitters in the forebrain, but there is increasing evidence for the role of endogenous opioid signaling in frontal cortex in nicotine reward as well.[44] Falling levels of dopamine and nicotine receptor stimulation lead to symptoms of withdrawal and prompt the urge to smoke.

Carbon monoxide has a very high affinity for hemoglobin and successfully competes with oxygen in binding to hemoglobin and forming carboxyhemoglobin. This presence of elevated levels of carboxyhemoglobin reduces the oxygen supply and produces hypoxemia. In order to compensate the low oxygen uptake, more red blood cells are generated, which leads to polycythemia. This increased blood viscosity leads to an increased risk of thrombus formation.

The oxidant gases present in tobacco smoke generate free radicals that initiate or aggravate endothelial inflammation and dysfunction, produce plasma lipid abnormalities (via oxidation of LDL-cholesterol) and stimulate platelet adhesion. Lipid peroxidation plays a central part in the development of foam cells, which contribute to atherogenesis as they accumulate within developing endothelial plaque.

The increase in myocardial oxygen demand (initiated by nicotine) and the decrease of the myocardial oxygen supply caused by increasing levels of carboxyhemoglobin and obstructions to flow produced by plaque development lead to myocardial ischemia.[32] Thousands of other chemicals are contained within tobacco smoke

and, when inhaled, augment and accelerate the development of atherosclerosis by inducing endothelial dysfunction; stimulating lipid oxidation; and coagulation mechanisms. [45, 46] Of the many constituents of tobacco smoke, at least 98 components of tobacco smoke have been found to produce measurable harm in humans.[47] Tobacco smoke also contains high concentrations of particulate matter, which have a known association with the risk of CVD.[48]

The mechanisms by which cigarette smoke causes CVD are linked synergistically. Active and passive cigarette smoke exposure alters the hemostatic process by disrupting the function of endothelial cells, platelets, fibrinogen, and coagulation factors. These imbalances of antithrombotic/ prothrombotic factors and profibrinolytic/antifibrinolytic factors support the initiation and propagation of thrombosis.[49] There is substantial evidence that inflammation and subclinical atherosclerosis are central to the pathophysiology of smoking-induced CVD.[50]

1.4 Environmental Tobacco Smoke or Second Hand Smoke and CVD risk

Passive or second hand exposure to tobacco smoke has a marked increase on the risk of CVD.[51-53]. Exposure to second hand smoke increases the risk of CHD by 20 to 30%.[51, 54] In fact, evidence suggests that sustained second hand smoke exposure is nearly as dangerous as direct tobacco use,[55] and causes 18 times more deaths from CVD than by lung cancer.[56]

Persons with CVD exposed to passive smoking experience an increase in heart rate, blood pressure, and carboxyhemoglobin; they typically experience a reduction in exercise capacity of approximately 20-40%.[57] The negative effects of passive smoking on platelets, endothelial progenitor cells, endothelial function, and cellular respiration have been documented in numerous studies.[55, 58, 59] Exposure to second hand smoking induces endothelial dysfunction, reduces vascular reactivity, and promotes hypertension.[60] Even brief exposure to second hand smoke adversely affects endothelial function, activates blood platelets, increases oxidative stress and the risk for thrombus formation and, as a consequence the risk of ischemic heart disease.[61]. A 50- to 60-percent increase in risk of CHD from exposure to second hand smoke has been documented in males.[62] In the INTERHEART study second hand smoking was associated with a graded increase in risk of myocardial infarction related to exposure; OR was 1.24 in individuals who were least exposed (1-7 h per week) and 1.62 in people who were most exposed (>21 h per week). The population attributable risk for exposure to SHS (more than 1 hour/ week) in never smokers was 15.4%.[63]

A 2016 review by the Cochrane Collaboration identified 44 studies which examined the association between public smoking bans and CVD health outcomes.[64] The risk of an acute myocardial infarction (AMI) has consistently been shown to decrease after the introduction of smoke-free legislation, and is revealed by a decline in hospital admissions for MI and reduced MI mortality rates.[64-66] An overwhelming body of knowledge supports

the central roles of smoking cessation and eliminating exposure to second hand smoke as fundamental to preventing the development and progression of CVD.[14, 51, 67]

RECOMMENDATIONS:

- Exposure to second hand smoke is nearly as dangerous as active tobacco use. Exposure to second-hand smoke should be eliminated or limited (Level of Evidence B).
- Smoke-free legislation has been clearly associated with population-level reductions in the incidence of myocardial infarction and CVD mortality and should be a priority in every country (Level of Evidence C).

1.5 Cardiovascular biomarkers and tobacco exposure

Numerous studies have identified serum biomarkers (e.g. C-reactive protein [CRP], interleukin [IL]-6, tumor necrosis factor [TNF], soluble TNF receptors [sTNFRs] I and II) that predict the risk of CVD.[68-72] Smoking promotes enhanced production of pro-inflammatory molecules and contributes to systemic inflammation as evidenced by elevated levels of inflammatory biomarkers. Specifically studies have documented an increase of the high-sensitivity C-reactive protein (hsCRP), a marker of systemic and vascular inflammation, among smokers.[50] Smoking has been also associated with increased levels of fibrinogen and coronary artery calcium (CAC).[73, 74]

A prospective study of 2,920 men from general practices in 24 British towns, aged between 60 and 79, with no history of CVD or diabetes, and no anticoagulant treatment, were compared regarding their smoking status. Current smokers had significantly increased levels of inflammatory markers (C-reactive protein, white cell count, fibrinogen), reduced albumin level, increased coagulation activation (fibrin D-dimer), increased levels of the endothelial marker, t-PA antigen, increased blood viscosity and hematocrit compared with never smokers. The strongest associations were seen with inflammatory factors: C-reactive protein, white cell count, and fibrinogen.[75]

Evidence regarding the impact of smoking on three domains of preclinical CVD (inflammation, vascular dynamics and function, and subclinical-atherosclerosis) was provided by the Multi-Ethnic Study of Atherosclerosis.[76] This rigorous cross-sectional examination of the impact of smoking involved 6,814 adults without prior CVD. Both former and current smoking status (confirmed by urinary cotinine) were independently associated with the following: 1) inflammatory biomarkers (high-sensitivity C-reactive protein [hsCRP], interleukin-6, and fibrinogen); 2) vascular dynamics and function (brachial flow-mediated dilation and carotid distensibility by ultrasound, as well as aortic distensibility by MRI; and, 3) subclinical atherosclerosis (coronary artery calcification, carotid intima–media thickness, and ankle-brachial index).[76] The high-sensitivity C-reactive (hsCRP) protein and coronary artery calcium (CAC) were both altered in smokers; a coronary artery calcium >100 and high-sensitivity C-reactive protein ≥3 mg/L identified higher relative risk among current smokers (e.g., all-

cause CHD hazard ratio of 3.0 [1.5–6.0, compared with CAC=0] and 2.6 [1.4–4.8, compared with high-sensitivity C-reactive protein <2 mg/L], respectively). It was also proven that even if both CAC>100 and hsCRP≥3 mg/L identify high-risk current smokers, CAC is a stronger CVD risk factor for many smoking subtypes (adjusted by status and pack-year category) and more frequently links smoking to events. Even current smokers with both CAC=0 and hsCRP<2 mg/L have relatively higher risk for events than non-smokers with normal levels of these risk markers.[36]

Carotid intima-media thickness, a marker of subclinical atherosclerosis and a commonly used predictor of CHD, and a surrogate end-point for CVD, AMI, and stroke is known to be influenced by active and passive smoking. [77-79] A Chinese study involving 722 patients with type 2 diabetes mellitus (338 women and 384 men) found that passive female smokers had a higher risk of CVD (Odds Ratio (OR) = 3.50, 95% confidence interval (CI): 1.29–9.49, P=0.009) when compared to non-smokers; they also had a significantly larger common carotid artery (P=0.041) and risk of carotid plaque (OR=2.20, 95% CI: 1.20–4.05, p=0.01). Both active and passive male smokers had a significantly greater carotid intima-media thickness than non-smokers (p=0.003 and p=0.005, respectively). Male active smokers had a significantly higher risk of carotid plaque (OR=2.88, 95% CI: 1.48–5.61, p=0.001).80

As in the described studies, it is obvious that cigarette smoking adversely modifies the level many of the CVD biomarkers, as evidenced by comparisons of smokers with non-smokers and former smokers; fewer studies have prospectively examined the reversal of such changes following smoking cessation. A pilot study examined associated inflammatory biomarkers in women with CVD risk during a smoking cessation program and demonstrated the rapid, positive consequences of smoking cessation as reflected in a reduction of the levels of these biomarkers.[81]

1.6 Benefits of smoking cessation for CVD

Smoking cessation is recognized as the single most powerful intervention for the prevention of CVD.[82] It is considered a "gold standard" preventative intervention in terms of its cost-effectiveness[83, 84] and is the only preventive strategy that results in cost-savings over a 30-year period.[85]

Within weeks of cessation a dramatic improvement in endothelial function, coagulation parameters, carboxyhemoglobin levels, lipoproteins, inflammatory status and circulatory function occurs.[81, 86] The risk of mortality from smoking-related heart disease for asymptomatic patients is dramatically reduced (to almost 50%) within 1 year of cessation.[16, 67, 87, 88]

Quitting smoking is also among the most effective secondary prevention measure, improving prognosis after a cardiac event.[89] In patients with CHD smoking cessation produces a significant reduction in the progression of existing disease, reduces hospital re-admissions, and results in lower morbidity and all-cause mortality.[90, 91] Among

CHD patients, smoking cessation is associated with a 32% reduction in the risk of nonfatal re-infarction and 36% reduction in mortality.[89, 92] Smoking cessation has been shown to result in a greater reduction in mortality than any other secondary prevention measure, including the use of β-blockers, angiotensin-converting enzyme inhibitors, statins or aspirin.[67, 92] Significant benefits emerge quickly after cessation and include: a decrease of carboxyhemoglobin levels, procoagulants, proinflammatory agents, inflammatory biomarkers, atherogenic lipoproteins and an improvement in endothelial and circulatory function.[45, 86]

A 20-year follow-up study of 1,041 consecutive patients who underwent first-time coronary artery bypass surgery showed that smoking cessation after surgery was an important independent predictor of a lower risk of death and coronary re-intervention during the study period in comparison to those patients who continued smoking.[87] Quitting smoking leads to a 40% reduction in mortality or readmission for patients with congestive heart failure93 In this patient population, the clinical benefits of cessation are equal to those of the pharmacological management of diminished ventricular function (beta-blockers or renin-angiotensin-aldosterone system inhibitors).[93, 94]

RECOMMENDATIONS:

- Smoking cessation should be a clinical priority for all CVD patients who smoke (Level of Evidence A).

1.7 Treating tobacco use as a high priority cardiovascular risk factor

Tobacco use is sadly treated with less importance and rigor when compared to other cardiovascular risk factors such as hypertension and dyslipidemia. Even patients at the highest risk typically do not receive assistance with smoking cessation. A study of 143,999 inpatients showed that compared to those without prior vascular disease, patients with prior vascular disease who presented with acute coronary syndromes were less likely to receive evidence-based smoking cessation treatments or cessation counseling.[95]

There has been a perception among clinicians that smoking is a 'lifestyle choice' or 'habit' rather than an addiction requiring treatment.[96] Although smoking cessation should be a priority for the secondary prevention of cardiac disease, cardiologists typically do not effectively address tobacco use as a clinical priority.[45]

The Fifth Joint Task Force (JTF) of the European Society of Cardiology (ESC) and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) consider changing smoking behavior as the cornerstone for improving CVD health, and that public health measures are crucial for changing the public's perception of smoking.[2] In order to improve the ESC program for CVD prevention, surveys are carried out to monitor the degree of guideline implementation in clinical practice. These surveys are called EUROASPIRE, and the hospital arm of the third survey showed that in 22 European countries large proportions of patients with CHD did not achieve the lifestyles, risk factor levels, and therapeutic targets set in 2003 by the third JTF. Smoking cessation treatment was provided to only 48% of CHD patients, com-

pared to the target of 100%. The EUROASPIRE III survey found that 30% of the participants were smokers up to the time of their coronary event and evidence-based treatment for smoking cessation was underused.[97]

Achieving cessation among patients may be challenging, due to the addictive nature of nicotine and the behavioural components surrounding tobacco use. Nevertheless, this should not deter clinicians from addressing tobacco use as a clinical priority in the management of CVD. Evidence-based treatment strategies exist which can significantly increase the success of quitting (See section 2.0). Given the significant impact of tobacco use on cardiovascular risk and its relative importance when compared to other CVD management strategies it is essential that tobacco use be considered with equal or greater importance as other CVD risk factors.

RECOMMENDATIONS:

- Health care professionals treating CVD patients should receive appropriate smoking cessation training and intervene with patients who smoke using evidence-based, best-practice treatment approaches (Level of Evidence A).

1.8 The need for incorporating systematic approaches to smoking cessation in routine primary and secondary CVD care

The evaluation of the smoking status of all patients, and the provision of cessation assistance should be priority in every cardiovascular setting (in-patient, out-patient).[35, 98-101]

While it has been demonstrated that smokers with CHD are more likely to spontaneously quit smoking compared to the general population of smokers, it must be noted that without assistance the majority of CHD patients are active tobacco users 1 year after a CHD-related hospitalization.[102, 103] A systematic approach to the identification and treatment of smokers, particularly in cardiac settings, can significantly enhance the likelihood of cessation.[104, 105]

Two approaches towards the prevention of CVD are well understood: the population strategy and the high-risk strategy.[106, 107]

The population strategy aims to reduce the CVD incidence at the population level through lifestyle and environmental changes, and is primarily achieved by establishing supportive policies and community interventions. One of the best-known examples is a smoke-free policy that includes smoking bans. Such a strategy brings large benefits to the population, and has a great impact on the number of cardiovascular events occurring within the population. The benefits of population approaches to smoking cessation may be large; all residents are targeted, and a majority of events occur in people who have only a modest CVD risk.

The high-risk approach aims to reduce smoking in those at the highest risk: persons as yet without CVD but with a high cardiovascular risk (and smoking distinctly elevates cardiovascular risk), and those with established

CVD. The individuals to whom such a strategy is applied receive great benefit, but the impact on the population level is limited, because the number of high-risk persons represents a small portion of the overall population. The population strategy has been considered for a long time as more cost effective than the high-risk approach, but some very useful interventions such as improvement in smoking cessation programs, increase the effectiveness of the high-risk approach.[108]

There is consensus that the largest preventive effect is achieved when such approaches are combined. Increased cardiovascular risk can begin at young age – smoking is a powerful indicator of increased cardiac risk. The systematic delivery of smoking cessation interventions to all smokers encountered in clinical settings allows for effective and efficient approaches to this major cardiovascular risk factor.

2.0
SMOKING CESSATION INTERVENTIONS EFFECTIVE IN CVD

2.1 Intervening with CVD Patients

A CVD event or diagnosis, in particular when associated with an invasive treatment such as coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty, or vascular surgery can serve to increase a patient's motivation to quit.[2] Such clinical events or encounters offer a unique opportunity to intervene with tobacco users, benefit from increased motivation to quit and can result in much higher rates of successful cessation.

The 5As (ask, advise, assess, assist, arrange) model for smoking cessation is recommended as a model for delivering tobacco treatment in clinical settings.[98, 106] The model recommends that all CVD patients be asked about their smoking status; that smokers, or those who have recently quit, be advised of the fundamental importance of cessation. Such advice is best delivered in a non-judgemental fashion, emphasizing the benefits of cessation while offering specific assistance with quitting. Clinicians can quickly assess a patient's desire to quit smoking and assist with developing a specific plan for quitting and arrange follow-up support.[2]

Clear, unequivocal, non-judgemental advice coming from physicians concerning smoking cessation is most important; it has been shown to increase the odds of successful cessation.109 The provision of pharmacotherapy to assist with cessation is now seen as central to contemporary, evidence-based cessation practice. A combination of pharmacotherapy and behavioural support yields the greatest benefits in quitting.[111] Strong evidence from randomized controlled clinical trials have documented the efficacy of both pharmacotherapy and behavioral support in supporting cessation among patients with CVD, as well as in the general population.[98, 106, 110]

RECOMMENDATIONS

- The "5As" (ask, advise, assess, assist, arrange) model for smoking cessation should be used with all CVD patients in all clinical settings (Level of Evidence A).
- The combination of pharmacotherapy and behavioral support is recommended for all CVD patients who smoke. There is strong evidence that the combination of such approaches produce greater efficacy than either used alone (Level of Evidence A).

2.2 Behavioural Interventions

Multiple randomized controlled clinical trials, in a variety of settings, have demonstrated the benefits of smoking cessation counseling for patients with CVD.[112, 113] The evidence for efficacy is strongest for patients who following an AMI.[114, 115]

Behavioral intervention tested to date have had great variability in terms of their content and methods of provision. These programs range from self-help methods, brief therapist-delivered interventions, such as advice from a physician, to more intensive or tailored behavioral interventions, such as group therapy or individual counselling (See Table 1).

TABLE 1: Types of Psychosocial Counseling Strategies

INTERVENTION TYPE	DESCRIPTION
Self-help	Includes print, video or online materials that provide self-directed support with quitting.
Brief Physician / Health Professional Advice	Verbal instructions from the physician or other health care professional with a 'quit smoking' message lasting 3-5 minutes.[109]

INTERVENTION TYPE	DESCRIPTION
Individual Counselling	Individual counseling is defined as more than 10 min face-to-face encounter between a patient and a counselor trained in assisting smoking cessation.[116]
Group Counselling	Small group based counseling support most often facilitated by a counselor trained in smoking cessation.
Telephone Counselling	Telephone services provide information and support for smokers often delivered by government funded 'help-lines', which may deliver proactive (counselor initiates) or reactive (smoker initiates) telephone contact.[117, 118]

A large review examined the efficacy of psychosocial interventions for smoking cessation in patients with coronary heart disease.[89] The review, which examined evidence published up to January 2013, included 40 randomized clinical trials (RCTs) and reported on intervention effects on both short-term (6 to 12 month follow-up) and long-term (more than 12 months) smoking abstinence. The review examined a variety of behavioral intervention approaches including telephone support and the provision of self-help material. The majority of trials involved older male patients with CHD -- predominantly AMI. The pooled analysis (n=7682, N=37) found a positive effect of psychosocial intervention on 6-12 month abstinence rates (risk ratio (RR) 1.22, 95% CI 1.13 to 1.32; abstinence rate treatment group = 46% vs. abstinence rate control group 37.4%). This translates to a 20% higher chance of quitting among patients receiving a psychosocial intervention compared to control. There was moderate heterogeneity between trials I2=54% and as such results should be interpreted with caution. The RRs for different types of psychosocial interventions were similar: (behavioral therapies RR 1.23, 95% CI 1.12 to 1.34; telephone support RR 1.21, 95% CI 1.12 to 1.30; self-help RR 1.22, 95% CI 1.12 to 1.33). As such no single strategy was shown to be superior. 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 month) did not appear effective (RR 1.01, 95% CI 0.91 to 1.12). More intense interventions (any initial contact plus follow-up over one month) produced a significant increase in quit rates (RR 1.28, 95% CI 1.17 to 1.40, I^2 58%). After one year, studies showed favorable effects of the smoking cessation intervention. Further research will aid in understanding the benefit of psychosocial interventions when delivered in combination with pharmacological therapy compared with pharmacological treatment alone.[89] A subsequent review by the Cochrane collaboration found the addition of behavioural support to pharmacotherapy increased

smoking abstinence by 10-25% compared to pharmacotherapy alone in the general population of tobacco users; it is likely similar outcomes could be expected among CVD patients.[111]

RECOMMENDATIONS:

- Psychosocial smoking cessation interventions should be provided to assist with cessation. They are effective in promoting abstinence provided they are of sufficient intensity and duration (Level of Evidence A).

2.3 Pharmacologic Interventions

The European Medicines Agency (EMEA) has approved three first line quit smoking medications: nicotine replacement therapy (NRT), varenicline and bupropion.[106] RCT evidence and systematic reviews have demonstrated the efficiency of these first-line therapies in promoting smoking cessation in the general population of smokers.[119, 120] These medications have different mechanisms of action and side effect profiles; all have undergone some scrutiny to identify potential cardiovascular effects of their use. None of the medications appear to raise the risk of serious CVD events.[121] Two second-line pharmacotherapies, Clonidine and Nortriptyline, have been identified as efficacious and may be considered by clinicians if first-line pharmacotherapies are not effective.

2.3.1. Nicotine Replacement Therapy

Efficacy

NRT is used to assist with reducing cravings and withdrawal when quitting. The medication is titrated over a period of 3-6 months. NRT is widely recommended and has been shown to increase rates of cessation at one-year follow-up by approximately 70% (OR 1.70, 95% CI 1.55-1.88).[122]

Safety

Outdated product warning labels which advise patients with CVD to speak to their physician before using NRT, have caused some confusion among both patents and clinicians about the use of NRT among CVD patients. There is strong evidence that NRT is safe for use in patients with CVD.[123] It is important to recognize that NRT is delivered via the venous system; while smoking delivers large quantities of nicotine, and almost 5,000 other chemicals, carcinogens and carbon monoxide to the left ventricle and hence to the arterial system. The use of NRT results in the delivery of markedly lower levels of nicotine and is therefore, arguably, much safer than continued smoking.

As described in section 1.3, nicotine may affect the cardiovascular system by increasing heart rate, blood pressure, and myocardial contractility, and reducing coronary blood flow. It is important, however, to note that

smokers become tolerant of nicotine's ability to induce cardiac effects. The dose of nicotine that follows the use of NRT products is much lower than that which follows smoking. [125] NRT has proven effective in supporting cessation and safe in patients with CVD.[124] Standard doses of NRT have no effect on physiologic coronary vasodilation.[123] A study based on nuclear perfusion imaging found that applying nicotine patch therapy reduces the extent of exercise-induced myocardial ischemia, suggesting that components of tobacco smoke other than nicotine are responsible for impaired coronary blood flow.[126] Others have demonstrated that the use of nicotine gum did not worsen endothelial function and did not reduce the cross-sectional area of the coronary arteries.[127]

Two major studies have included participants with cardiovascular diagnoses and found no increased risk of CVD in smokers who used NRT.[128, 129] The Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease (n=156) and a study by Joseph et al (n=584) determined there was no significant increase in cardiovascular events in 2 high-risk populations with cardiac disease when nicotine patch users were compared with placebo patch users. In order to evaluate any connection between NRT and an increased risk of AMI, acute stroke, or death, a self-control case series analysis of data from The Health Improvement Network (THIN) was performed.[130] In total 33,247 patients with at least one prescription for NRT between June 1985 and November 2003 were identified. There was a progressive increase in the incidence of first AMI in the 56 days leading up to the first NRT prescription (overall incidence ratio 5.55, 95% CI 4.42 to 6.98), but the incidence fell after this time and was not increased in the 56 days after starting NRT (incidence ratio 1.27, 95% CI 0.82 to 1.97). The results were similar for second AMI and stroke, and for subgroups of people with pre-existing angina and hypertension. There was no evidence of increased mortality in the 56 days after the NRT prescription (incidence ratio 0.86, 95% CI 0.60 to 1.23). The conclusion of the authors was that the use of NRT is not associated with any increase in the risk of AMI, stroke, or death.[130]

Acute Coronary Syndromes

The package insert for NRT recommends caution in patients with acute cardiovascular diseases. This is primarily because most initial studies specifically excluded patients with acute coronary syndromes when the drugs clinical efficacy was being evaluated. Since this time the question of safety in this population of patients has been studied and no evidence of increased risk has been documented.[90, 125, 131-135] Woolf 2012 evaluated 663 smokers with acute coronary syndromes, separated into the NRT (184 patients) or control (479 patients) groups according to whether NRT was prescribed on hospital discharge.[123] Of the 663 patients, 202 had adverse events in the first year after the acute coronary syndrome, but no significant differences were seen with NRT use for the 1-year combined end point of death, AMI, repeated revascularization, or re-hospitalization for angina, congestive heart failure or arrhythmia (OR 0.89, 95% CI 0.61 to 1.30, p=0.54), thus proving that NRT use after acute coronary syndromes was not associated with an increased risk of adverse cardiovascular events. While there is

no evidence to suggest safety concerns with the use of NRT in this population of CVD patients, additional research is required to increase the strength of this evidence.

RECOMMENDATIONS:

- NRT is an effective first line smoking-cessation medication. It is safe to use in patients with stable CVD (Level of Evidence A).
- There is no evidence to suggest safety concerns with the use of NRT among patients with acute coronary syndromes patients. Additional research is required to increase the strength of this evidence (Level of evidence D).

2.3.2 Bupropion

Bupropion is an aminoketone approved in 1989 for the treatment of depression and in 1997 for smoking cessation. Its mechanism of action in supporting smoking cessation is not completely understood; it is felt that it acts by inhibiting the neuronal uptake of norepinephrine and dopamine.[136] Bupropion may also block the activity of nicotinic acetylcholine receptors.[137] Its mechanism of action for smoking cessation appears to be unrelated to its antidepressant properties.[138]

The major risk of bupropion is a reduction of the seizure threshold. The risk of seizure from the sustained-release formulation of bupropion is 0.1 percent -- no different from that of other antidepressants.[106] No seizures were reported in any of the clinical trials that examined the effects of sustained-release bupropion in assisting with smoking cessation.

Evidence from several randomized, placebo-controlled trials shows that bupropion doubled the smoking cessation rates in a general population of tobacco users producing ORs of 1.62 (95% CI 1.49–1.76).[139]

As with NRT, early case reports of serious cardiovascular events with sustained-release bupropion raised questions about the safety of this agent in patients with CVD. These reports, which were mostly in Canada and England, included cardiac deaths, chest pain, AMI, and myocarditis[140] Assessment of the contribution of bupropion to these events is difficult because an evaluation of other cardiac risk factors in these patients was not possible. To date, none of the efficacy trials of bupropion for smoking cessation have reported a significant increase in cardiovascular events. Dizziness, high blood pressure, and thoracic pain may appear as rare adverse effects. Blood pressure monitoring is advised, especially if therapeutic combinations are used, e.g. when combining the use of bupropion and nicotine patches.[106]

Sustained-release bupropion is effective and safe for treating smokers with stable CVD[141,142] The drug appears to be less efficacious in smokers hospitalized with acute CVD than in other groups of patients.[143] Bupropion has been tested in patients with acute CVD; it appears to be safe for those with either stable or acute disease.[143, 144]

A multi-center, randomized, double blind, placebo-controlled study of bupropion in subjects from 28 centres across 10 countries enrolled adults who smoked an average of ≥10 cigarettes/day during the previous 12 months and who had not made a serious attempt to stop smoking using nicotine replacement therapy during the previous 3 months.[142] Subjects were motivated to stop smoking and had at least one of the following cardiovascular conditions: AMI >3 months ago, interventional cardiac procedure >3 months ago, stable angina pectoris, peripheral vascular disease or congestive heart failure (NYHA Class I or II). In total, 629 participants were enrolled, however 120 (38%) patients in the bupropion SR group and 155 (50%) receiving placebo prematurely discontinued treatment after 52 weeks. At 6 and 12 months after beginning treatment, subjects who had received bupropion SR were significantly more likely to have successfully stopped smoking than those receiving placebo. After 7 weeks of bupropion SR treatment, more than twice as many smokers with CVD had quit smoking at 1 year compared with placebo.[142] Bupropion SR was well tolerated and the safety profile was very good, more favorable than expected for a study population of this type. In total, 38 subjects (6%) reported cardiovascular adverse events (bupropion SR n=24; placebo n=14). The most common were angina pectoris (bupropion SR n=7; placebo n=4), hypertension (bupropion SR n=2; placebo n=3), and palpitations (bupropion SR n=4; placebo n=1).

A multi-centre randomized double-blind placebo-controlled trial conducted in five hospitals assessed the safety and efficacy of 12 weeks of sustained-release bupropion (300 mg) or placebo in 248 smokers admitted for acute CVD, primarily AMI and unstable angina. Validated tobacco abstinence rates in bupropion and placebo groups were 37.1% vs. 26.8% (OR 1.61, 95% CI, 0.94-2.76; p=0.08) at 3 months and 25.0% vs. 21.3% (OR, 1.23, 95% CI, 0.68-2.23, p=0.49) at 1 year. The adjusted OR, after controlling for cigarettes per day, depression symptoms, prior bupropion use, hypertension, and length of stay, was 1.91 (95% CI, 1.06-3.40, P=0.03) at 3 months and 1.51 (95% CI, 0.81-2.83) at 1 year. Bupropion and placebo groups did not differ in cardiovascular mortality at 1 year (0% vs. 2%), in blood pressure at follow-up, or in cardiovascular events at end-of-treatment (16% vs. 14%, incidence rate ratio 1.22 (95% CI: 0.64-2.33) or 1 year (26% vs. 18%, IRR 1.56, 95% CI 0.91-2.69). The investigators concluded that bupropion improved short-term, but not long-term, smoking cessation rates when compared to intensive counseling and appeared to be safe in hospitalized smokers with acute CVD.[144]

A recent multicenter, double-blind, placebo-controlled, randomized trial in 392 smokers hospitalized with AMI revealed that bupropion is well tolerated and appears safe to use in the immediate post-AMI period.143 A large network meta-analysis performed by Mills found a protective effect with bupropion (RR, 0.45; 95% CI, 0.21–0.85) on major adverse cardiovascular events.[121] The potential cardio-protective role of bupropion is not well understood, but it is possible that the antidepressant origins of bupropion reduce vascular stress.[145, 146] It must be recognized that any successful smoking cessation intervention is likely to be associated with a reduction in cardiovascular events – given the deleterious effects of continued smoking on cardiovascular health. In-

creased attention is recommended when using medicines, which may interact with bupropion; caution is advised when using drugs that induce or inhibit the enzyme 2D6 or the P 450 structures. The use of bupropion may increase the bioavailability of metoprolol and some anti-arrhythmic medication like propaphenone. Monitoring blood pressure is also recommended.106 It must always be remembered that the risks associated with the use of any smoking cessation medication must be compared to the considerable risks associated with continued smoking.

RECOMMENDATIONS:

- Bupropion improves smoking cessation rates and is safe for use in patients with CVD including those with acute cardiovascular disease (Level of Evidence C).
- Monitoring of blood pressure is recommended when using bupropion. This may be of particular importance when using combination cessation therapy e.g. bupropion with nicotine patches (Level of Evidence C).
- Caution is needed in case of: simultaneous use of medication that might interact with bupropion such as drugs that induce or inhibit the enzyme 2D6 of the P450 structures; and, the use of bupropion with metoprolol and certain anti-arrhythmic medications like propaphenone, which may increase the bioavailability of such medications. (Level of Evidence C).

2.3.3 Varenicline

Varenicline tartrate is the first non-nicotine medication approved for smoking cessation in over a decade.[147] Varenicline is a partial agonist of the alpha4 beta2 nicotinic acetylcholine receptor, and reduces the symptoms and signs of nicotine withdrawal. Simultaneously, by occupying the receptor site, it prevents nicotine from attaching to the receptor thereby diminishing nicotine's ability to produce its characteristic responses..[147] Varenicline produces approximately 50 percent of the receptor stimulation provided by nicotine, but it blocks many of the effects of nicotine produced by cigarette smoking.

Clinical trials have found varenicline to be superior to bupropion and standard doses of NRT in promoting smoking cessation.[91, 148-150] Prolonged administration has been shown to reduce relapse in smokers who had been abstinent 12 weeks after initial therapy.[151] In 2010 Rigotti, Pipe et al. reported the efficacy of varenicline versus placebo in 714 smokers with stable cardio-vascular diseases.[152] The authors found a continuous abstinence rate higher with varenicline (47.0% versus 13.9%) in weeks 9-12, as in weeks 9-52 (19.2% v. 7.2%).

In a meta-analysis of the safety of varenicline, Singh and colleagues raised concerns of an increased risk of serious adverse cardiovascular events among individuals using varenicline.[153] The Singh meta-analysis and its conclusions, however, have been widely criticized in the literature as a result of concerns that inappropriate analysis techniques were employed.[154-159] Several reviews have since dismissed their conclusions. Prochaska and

Hilton conducted a systematic review and meta-analysis of treatment emergent, cardiovascular serious adverse events in all randomized controlled trials of varenicline published from January 2005 (the year when articles on varenicline were first published) to September 2011. Twenty-two randomized controlled trials of varenicline's use in smoking cessation were identified; all were double-blind and placebo controlled, and included 9,232 participants (5431 randomized to varenicline, 3801 to placebo). The crude rates of treatment emergent, cardiovascular serious adverse events were 0.63% (34/5431) in the varenicline group and 0.47% (18/3801) in the placebo group. No events occurred in eight trials, including three trials with more than 100 participants per arm. This meta-analysis of 22 independent trials involving more than 9000 individuals had high power to detect a significant treatment effect and found negligible variation in the evidence across the trials. The authors concluded that no serious adverse cardiovascular events were associated with varenicline use.[160]

Most recently, Mills et al. aimed to examine the comparative safety of NRT, bupropion, and varenicline, evaluating all CVD events and major adverse cardiovascular events, defined as cardiovascular death, nonfatal AMI, and nonfatal stroke reported in published RCTs and FDA reports in smokers with and without pre-existing CVD.121 The review covered the period up to March 20 2013 and included RCTs that studied one or more of the 3 treatments that reported CVD outcomes. In the18 eligible studies involving varenicline, there was no evidence of harm with varenicline (RR, 1.34; 95% CI, 0.66–2.66).

RECOMMENDATIONS:

- Varenicline has been shown in experimental studies to be more effective than bupropion and standard dose nicotine patches in promoting smoking cessation (Level of Evidence A).
- The risk of serious adverse cardiovascular events associated with varenicline use is small, and considered statistically and clinically insignificant (Level of Evidence A).

2.4 Delivering systematic interventions for smoking cessation to CVD patients

Systematic approaches to the identification of smokers; the provision of clear, unambiguous advice regarding the importance of smoking; and, a specific offer of assistance with cessation can significantly increase the likelihood of cessation. The delivery of such an approach, in all professional settings, is increasingly seen as a standard of care. The same diligence with which latent hypertension, occult dyslipidemia and undiagnosed diabetes are pursued should now be applied to identify smokers and assist them in addressing their nicotine addiction – with an expectation of significant improvements of cardiovascular health. Such systems should involve formal hospital policies and the identification of roles and responsibilities of clinical team members in tobacco treatment delivery including cardiovascular specialists, nurses and other health professionals. **Table 2** provides a summary of recommendations for healthcare professionals working with cardiovascular patients.[101]

TABLE 2: Summary of recommendations for cardiovascular specialists

RECOMMENDATIONS
Introduce a systematic approach to smoking cessation in all professional settings.
Become familiar with the principles and practice of smoking cessation, including the use and prescription of validated pharmacotherapies (NRT, bupropion, varenicline).
Identify and document the smoking status of all patients.
Provide clear, concise, unambiguous, and non-judgmental advice regarding the importance of cessation.
Offer specific assistance in initiating a cessation attempt.
For hospitalized smokers, commence interventions for smoking cessation during the period of hospitalization and facilitate ongoing follow-up.
Provide clinical leadership to trainees and colleagues in the appropriate management of the tobacco-addicted patient.
Advocate for public policies to appropriately control all tobacco products.

Source: Pipe AL, Eisenberg MJ, Gupta A, Reid RD. Smoking Cessation and the Cardiovascular Specialist: Canadian Cardiovascular Society Position Paper. Canadian Journal of Cardiology 2011;27:132–137.

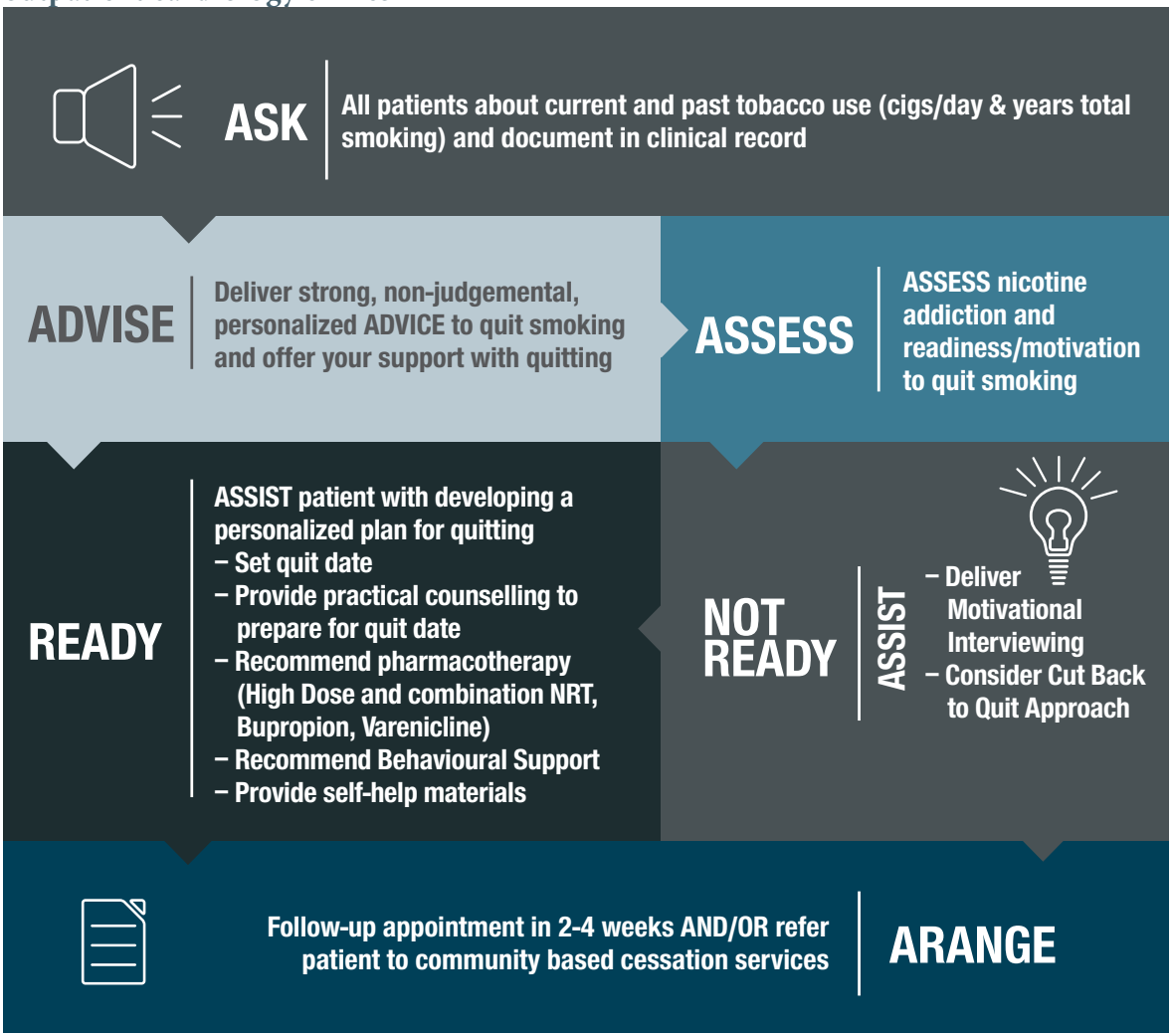
2.4.1 Primary care settings, including physicians' and dentists' offices

Primary care settings, including general practice and dental offices, provide the opportunity to screen CVD patients for tobacco use and support cessation. Physicians and other health care professionals can be powerful agents for supporting smoking cessation.[109] Patients are more likely to be thinking about their health and the possible negative consequences of smoking when they are in a physician's office or in hospital than in any other settings. The advice of one's own physician is highly valued by the majority of patients, and evidence demonstrates that smokers believe that their doctor's intervention will increase their success with cessation.161 Randomized clinical trial evidence has that even a few minutes of advice to quit smoking from a physician or dentist) can have a significant impact on prompting and sustaining cessation.[109] Figure 2 presents the recommended protocol for intervening with smokers in the primary care setting.

RECOMMENDATIONS:

- Primary care providers should assess the smoking status of, and deliver evidence based smoking cessation treatments to, all patients with a CVD diagnosis or at risk of CVD as a priority (level of evidence A).

FIGURE 2: Tobacco Treatment Protocol for CVD patients in primary care and outpatient cardiology clinics



2.4.2 Secondary care/ hospitalized patients

Hospitalization, especially for a tobacco-related disease, can serve as a "teachable moment" in which motivation to quit and patient's receptivity to cessation advice and assistance may increase. The smoke-free environments provided by hospitals also provide an opportunity for tobacco users attempt cessation away from the usual environmental cues to smoke.

Behavioral smoking cessation interventions, initiated during hospitalization, have been found to result in significantly higher rates of smoking abstinence when compared to usual care.[162]

A Cochrane review by Rigotti et al. examined the effectiveness of interventions for smoking cessation that are initiated for hospitalized patients. Fifty randomized and quasi-randomized trials were identified of behavioral, pharmacological or multi-component interventions to help hospitalized patients stop smoking. The analysis of the fifty trials conducted in acute care hospitals indicated:

- Intensive counselling interventions that begin during hospitalization and continue for at least one month following discharge increase smoking cessation rates after discharge (RR 1.37, 95% CI 1.27 to 1.48; 25 trials);
- Adding nicotine replacement therapy (NRT) to an intensive counselling intervention increased smoking cessation rates compared with intensive counselling alone (RR 1.54, 95% CI 1.34 to 1.79, six trials);
- Adding varenicline to intensive counselling had a non-significant effect in two trials (RR 1.28, 95% CI 0.95 to 1.74);
- Adding bupropion did not produce a statistically significant increase in cessation compared to intensive counselling alone (RR 1.04, 95% CI 0.75 to 1.45, three trials);

The Rigotti review examined trials that reported on the subgroup of smokers admitted to hospital because of CVD and found similar results to the general populations of tobacco users. In this subgroup analysis, intensive intervention with follow-up support increased the rate of smoking cessation (RR 1.42, 95% CI 1.29 to 1.56).

A recent study of 302 smokers hospitalized with an acute coronary syndrome who were randomized to receive either counselling plus 12 weeks of varenicline treatment or counselling alone found that the varenicline group had significantly higher seven-day point prevalence smoking abstinence rates at three months (57.7 per cent vs. 36.4 per cent) and six months (47.3 per cent vs. 32.5 per cent).[163]

A Canadian study of intensive intervention including counselling and pharmacotherapy for smokers admitted to hospital 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.[164]

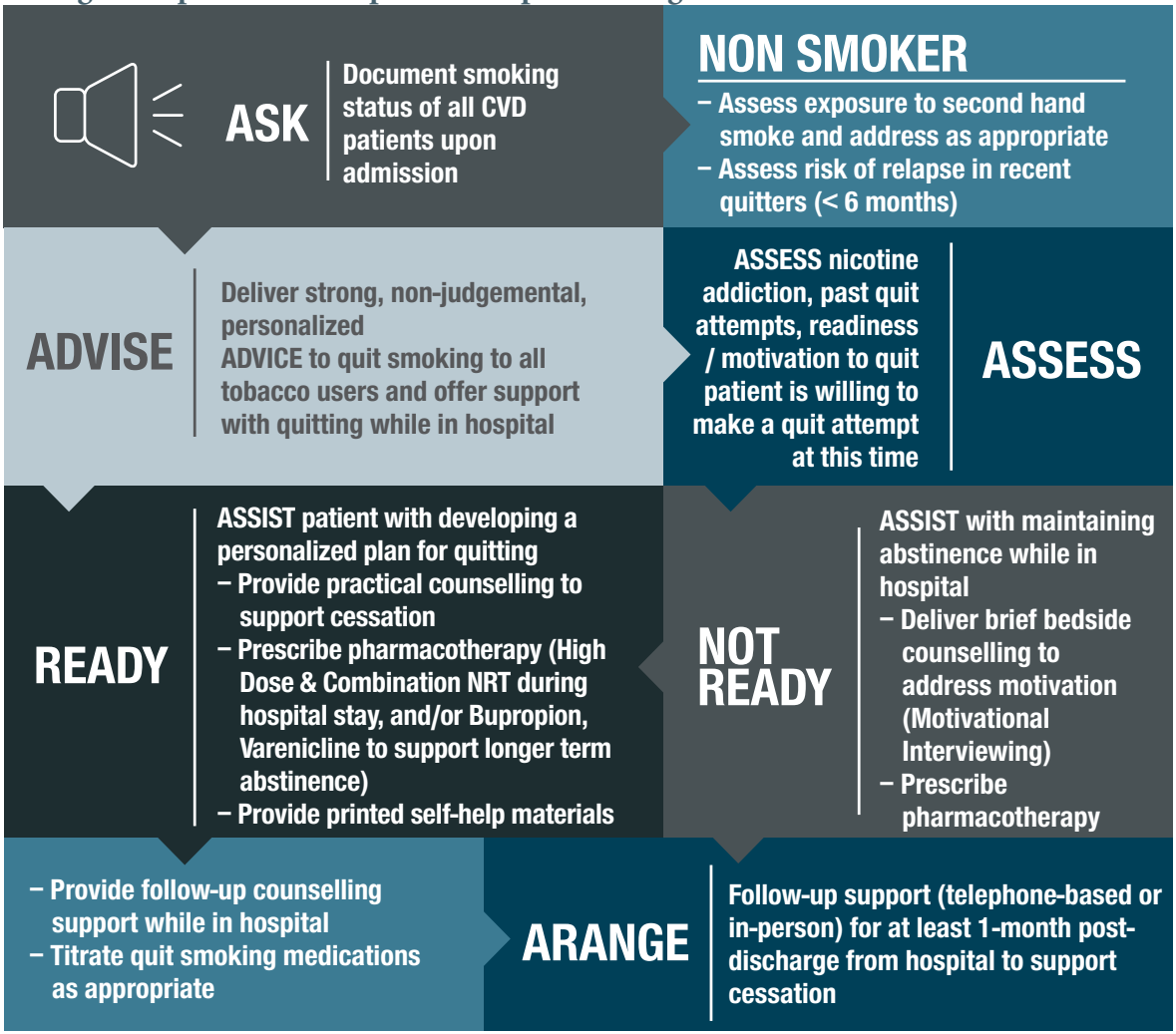
In summary, there is strong evidence to show interventions that combine the provision of NRT with behavioural counseling beginning during hospitalization and including at least one month of supportive post-discharge are most effective for smoking cessation in hospitalized patients. There was no evidence of effect for in-

terventions of lower intensity or shorter duration.[162] There is emerging evidence to suggest that varenicline combined with behavioural counseling may increase success with quitting among patients hospitalized with CVD.

RECOMMENDATIONS:

- Among patients hospitalized with a CVD-related illness, smoking cessation interventions should be initiated during hospitalization as a standard of care (Level of Evidence A).
- Including at least one month of supportive post-discharge contacts will further increase rates of cessation (Level of Evidence A).
- Adding NRT to intensive counselling significantly increases cessation rates over counselling alone (Level of Evidence A).
- There is emerging evidence that varenicline and intensive counseling may be superior to counseling alone among hospitalized CVD patients, however further studies are needed to strengthen this recommendation (Level of Evidence B).

FIGURE 3 presents the recommended protocol for intervening with tobacco users among CVD patients in in-patient hospital settings



3.0
SMOKING CESSATION IN CVD SUB-POPULATIONS

3.1 Hypertensive patients

Cigarette smoking and hypertension are two of the most important cardiovascular risk factors, for the reduction of CVD morbidity and mortality.165,166 Both smoking and hypertension are each accompanied by at least a 2-to 3-fold increase in risk for cardiovascular events.[167,168] When acting together, smoking and hypertension synergistically increase cardiovascular risk.19,169 Smoking cessation is essential for promoting cardiovascular health among hypertensive patients.

A recent study on 305 previously untreated hypertensive subjects found smokers and ex-smokers showed lower reduction than non-smokers for systolic BP (4±1.7 vs. 13.6±1 vs. 17.6±1) and diastolic BP (6.5±1.0 vs. 8.7±0.8 vs. 10±0.7, $p<0.01$) respectively.170 Baseline systolic blood pressure, smoking status and female gender were the only significant predictors of fall in systolic BP ($R2=0.19$, $p<0.0001$). This study provides evidence that smoking reduces the response to anti-hypertensive treatment, independent of age, gender and body mass index. Smoking cessation reduced cardiovascular risk and also improved control in hypertensive patients.[126]

A longitudinal study comparing the mortality risks of smokers vs. non-smokers in a large cohort of workers in Taiwan (n = 23,755 with a 17-year follow-up) reported on the excess mortality risks of smoking when converted into a 'blood pressure equivalence'. The increase mortality risk of active smoking was found to be equivalent to an increase in blood pressure of 40 mmHg.[171] Meaning that smoking cessation in hypertensive patients could provide a reduction of mortality risks similar to a permanent reduction of 40 mmHg in blood pressure, over and above any anti-hypertensive medications.[171] In a sample of 20,202 adults participating in the Health Survey for England, current smokers with defined hypertension were significantly less aware of their hypertension than hypertensive past or never smokers: only half of hypertensive smokers reported having received a diagnosis with hypertension [51.3%, 95% confidence interval (CI): 48.8-53.8]. Smokers aware of their hypertension were more likely to have received advice to stop smoking (OR: 3.29, 95% CI: 2.59-4.18) and stopped smoking (OR: 1.58, 95% CI: 1.32-1.89) than smokers unaware of their hypertension.[172]

There is clear evidence that the treatment of hypertension in smokers does not result in as great a benefit in

risk reduction as might be assumed. Continued smoking negates many of the anticipated reductions in risk normally associated with the management of hypertension.

RECOMMENDATIONS:

- Aggressive management of tobacco use among hypertensive patients will significantly reduce CVD risk and should be a clinical priority (Level of Evidence B).

3.2 Peripheral arterial disease

Atherosclerotic peripheral arterial disease (PAD) is a highly prevalent disorder that affects between 5-10% of adults, and is a major cause of disability.[173-175] PAD progresses to decreased functional capacity and, if untreated, leads to critical limb ischemia, (defined as ischemic rest pain, gangrene, or amputation). Although those with PAD, even if asymptomatic, have an increased risk of future cardiovascular events and related mortality, PAD is a commonly overlooked condition in primary care settings, because most patients are asymptomatic.[176] Cigarette smoking is the single most important risk factor for the development and progression of PAD and a meta-analysis of 17 studies found a 2.2-fold greater prevalence of symptomatic PAD in smokers compared with nonsmokers.[177] Continuing to smoke accelerates the progression of stable claudication to serious ischemic syndromes, such as critical limb ischemia, and to systemic cardiovascular ischemic events (e.g., angina, AMI, transient ischemic attack, and stroke). PAD smokers who manage to quit tobacco use have far higher survival rates than those who do not.[178]

Many patients with PAD who are current smokers are interested in quitting and receptive to a formal smoking cessation program; a significant proportion of them will quit if provided with adequate support. A study conducted in two medical centers in Minneapolis randomized 124 patients with PAD to either an intensive intervention group (6 counseling sessions over a period of 5 months) or to a minimal intervention group.[179] Participants assigned to the intensive intervention group were significantly more likely to be confirmed abstinent at 6-month follow-up: 21.3% versus 6.8% in the minimal intervention group ($p=0.023$).[179]

A study on 2517 community-dwelling Korean men aged 50 years and older that employed information on smoking characteristics such as smoking status, pack-years of smoking, and years since cessation found out that cumulative smoking exposure and duration of smoking cessation were significantly associated with PAD in middle-aged and older Korean men.[180] Available evidence suggests that it is not cost effective to commence patients on anti-platelet and lipid-lowering agents if they continue to smoke.[181]

RECOMMENDATIONS:

- All PAD patients should be offered support with smoking cessation that includes counseling and first-line quit smoking medications (Level of Evidence B).

3.3 Women

Although historically rates of tobacco use were higher among men, rates of tobacco use have increased among women and in some countries have surpassed those of males.[2] It is estimated that 250 million women and 1 billion men are daily tobacco users worldwide.[182] The proportion of female smokers is estimated to increase from 12% in the first decade of this century to 20% by 2025.[182]

The risk associated with smoking has been found to be higher in women compared to their male counterparts.[183,184] and different explanations have been proposed to explain these differences including:

- women metabolize nicotine more rapidly than men, especially women taking oral contraceptives[185] with possible effects on compensatory smoking.
- smoking may have an adverse effect on estrogen.[186]

Women who use oral contraceptives and smoke cigarettes have a synergistically increased risk for both AMI and stroke.[185] Additionally, women are frequently exposed to passive smoke. Many non-smoking women for example suffer increased risk of CVD and lung cancer from exposure to secondhand smoke produced by their husbands or partners.[51]

3.4 Elderly CVD Patients

It has been clearly demonstrated that smoking cessation is of benefit at any age.[187] Despite the fact that most cardiovascular events occur in older adults, this age group has been understudied when it comes to the cardiovascular risks of smoking and the potential cardiovascular benefits of smoking cessation. A large meta-analysis using data from 25 cohorts from across Europe and the United States corroborated and expanded evidence from previous studies to show that smoking is a strong independent risk factor for cardiovascular events and mortality among older adults.[188] Meta-analysis data drawn from [503,905] participants aged 60 and older found the association of smoking status with cardiovascular mortality yielded a hazard ratio of 2.07 (95% CI 1.82 to 2.36) for current smokers and 1.37 (95% CI 1.25 to 1.49) for former smokers when compared to never-smokers. The excess risk in smokers was dose-dependent with cigarette consumption, and decreased continuously with time since smoking cessation in former smokers. Considering the increasing numbers of older people and the higher incidence of cardiovascular events and mortality at older age, there is a huge potential for smoking and CVD prevention in this patient population.[188]

A population-based cohort study that examined the lifetime smoking history of 8,807 people from Germany aged between 50–74 years without a previous AMI or stroke.189 Compared to never smokers, the adjusted hazard ratios (95% CI) of current smokers was 2.25 (1.62-3.12) for MI, 2.12 (1.65-2.73) for stroke and 2.45 (1.76-3.42) for CVD compared to never smokers. Risk advancement periods were 19.3, 9.8 and 8.4 years for MI, stroke and CVD, respectively for smokers compared to never smokers. A clear dose-response relationship was found for both current and lifetime amount of smoking. Quitting smoking resulted in elimination of most of the excess CVD risk as well as in risk advancement within the 5 years period following smoking cessation. The study offers evidence that smoking is an important risk factor for cardiovascular at any age, and that smoking cessation is always highly and rapidly beneficial regardless of age.[189]

In a study comparing cardiovascular and mortality risks in elderly patients treated with varenicline (n=74,824) or bupropion (n=14,133) the adjusted hazard ratios (95% CI) were 0.79 (0.50–1.24) for AMI, 1.27 (0.63-2.55) for stroke, 0.58 (0.30-1.13) for death, 0.84 (0.58-1.23).[190] A very recent study assessed data from the Cooperative Cardiovascular Project, a medical record study of 158,349 elderly Medicare patients with AMI and over 17 years of follow-up, in order to evaluate the age-specific association of smoking with life expectancy and years of life lost after AMI. Current smokers had lower crude mortality up to 5 years because of their younger age at AMI. After adjusting other patient characteristics, tobacco use was associated with lower 30-day mortality (hazard ratio 0.91, 95% CI 0.87 to 0.94) but higher long-term mortality (17-year HR 1.19, 95% CI 1.17 to 1.20) after AMI. Overall, life expectancy estimates were lower for current smokers than non-smokers at all ages, and as age at AMI increased, the magnitude of life-years lost due to smoking decreased. After full risk adjustment, the differences in life expectancy between current smokers and non-smokers persisted at all ages. This study brings new evidence for the high necessity of smoking cessation efforts after AMI in the elderly.[191]

RECOMMENDATIONS:

- Smoking cessation is highly and rapidly beneficial for the reduction of CVD risk at all ages and should be a priority within every age group (Level of Evidence A)

REFERENCES

1. Mendis S., Puska P., Norrving B. Global Atlas on cardiovascular disease prevention and control. Geneva: World Health Organization (WHO), World Heart Federation (WHF), World Stroke Organization (WSO); 2011.
2. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). European heart journal. 2012;33(13):1635-701.
3. Kumar G, Mohan S, Yadav L, Arora M. Global tobacco surveys: information for action by cardiologists. Global heart. 2012 Jul;7(2):99-105.
4. ITC Project, WorldHealthOrganization (WHO), WorldHeartFederation (WHF). Cardiovascular harms from tobacco use and secondhand smoke: Global gaps in awareness and implications for action. Waterloo, Ontario, Canada and Geneva, Switzerland; 2012.
5. Arora M, Millett C, Reddy KS. Tobacco and CVD: Challenges and Opportunities. Global heart. 2012 Jul;7(2):95-8.
6. WHO. Global status report on noncommunicable diseases 2010. Geneva; 2010.
7. WHO. WHO REPORT ON THE GLOBAL TOBACCO EPIDEMIC, 2011: Warning about the dangers of tobacco. 2011.
8. WHO. Cardiovascular diseases (CVDs). 2011 [cited; Available from: http://www.who.int/mediacentre/factsheets/fs317/en/
9. Scottish Intercollegiate Guidelines Network (SIGN). Risk estimation and the prevention of cardiovascular disease: A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network 2007.
10. Doll R, Peto R, Boeham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004;328(7455):1519.
11. Burns DM. Epidemiology of smoking-induced cardiovascular disease. Prog Cardiovasc Dis. 2003(46):11-29.
12. Figure entitled " Attributable deaths due to selected risk factors (in thousands). From: Global atlas on cardiovascular disease prevention and control
Page: 19 Figure: 29 - ISBN 978 92 4 156437 3 - http://apps.who.int/iris/handle/10665/44701
13. Edwards R. The problem of tobacco smoking. BMJ. 2004(328):217-9.
14. Goldenberg I, Jonas M, Tenenbaum A, et al. Current smoking, smoking cessation, and the risk of sudden cardiac death in patients with coronary artery disease. Arch Intern Med 2003;163(19):2301-5.
15. He J, Ogden LG, Bazzano LA, Vupputuri

S, Loria C, Whelton PK. Risk Factors For Congestive Heart Failure In US Men And Women: NHANES I Epidemiologic Follow-Up Study Arch Intern Med 2001(161):996-1002.
16. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. American Heart Association Task Force on Risk Reduction. Circulation. 1997;96(9):3243-7.
17. Pujades-Rodriguez M, George J, Shah AD, et al. Heterogeneous associations between smoking and a wide range of initial presentations of cardiovascular disease in 1937360 people in England: lifetime risks and implications for risk prediction. Int J Epidemiol. 2015;44(1):129-41.
18. Schroeder SA. New evidence that cigarette smoking remains the most important health hazard. N Engl J Med. 2013(368):389–90.
19. U.S. Department of Health and Human Services. The Health Consequences of Smoking: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Pevention and Health Promotion, Office on Smoking and Health; 2004.
20. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, et al. Effect Of Potentially Modifiable Risk Factors Associated With Myocardial Infarction In 52 Countries (The INTERHEART Study): Case-Control Study. Lancet 2004(364):937-52.
21. Mähönen MS, Mcelduff P, Dobson AJ, Kuulasmaa KA, A E. Current smoking and the risk of non-fatal myocardial infarction in the WHO MONICA Project populations. Tob Control 2004(13):244-50.
22. Parish S, Collins R, Peto R, et al. Cigarette Smoking, Tar Yields, And Non-Fatal Myocardial Infarction: 14,000 Cases And 32,000 Controls In The United Kingdom. The International Studies Of Infarct Survival (ISIS) Collaborators. BMJ 1995(311):471-7.
23. Centers for Disease Control and Prevention. Smoking and tobacco use: health effects of cigarette smoking. 2012 [cited; Available from: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/index.htm
24. Wilhelmsson C, Vedin JA, Elmfeldt D, Tibblin G, Wilhelmsen L. Smoking and myocardial infarction. Lancet. 1975(1):415–20.
25. Rosenberg L, Kaufman DW, Helmrich SP, Miller DR, Stolley PD, Shapiro S. Myocardial infarction and cigarette smoking in women younger than 50 years of age. JAMA. 1985(253):2965–9.
26. Hartz AJ, Barboriak PN, Anderson AJ, Hoffmann RG, Barboriak JJ. Smoking, coronary artery occlusion and nonfatal myocardial infarction. JAMA.

REFERENCES

1981(246):851–3.

27. Mulcahy R, Hickey N, Graham IM, MacAirt J. Factors affecting the five-year survival rate of men following acute coronary heart disease. Am Heart J 1977(93):556 –9.
28. Muscat JE, Harris RE, Haley NJ, Wynder EL. Cigarette Smoking And Plasma Cholesterol. Am Heart J. 1991(121):141-7.
29. Campisi R, Czernin J, Schöder H, et al. Effects Of Long-Term Smoking On Myocardial Blood Flow, Coronary Vasomotion,And Vasodilator Capacity. Circulation. 1998(98):119-25.
30. Fusegawa Y, Goto S, Handa S, Kawada T, Ando Y. Platelet Spontaneous Aggregation In Platelet-Rich Plasma Is Increased In Habitual Smokers. Thromb Res. 1999.
31. Hung J, Lam JY, Lacoste L, Letchacovski G. Cigarette Smoking Acutely Increases Platelet Thrombus Formation In Patients With Coronary Artery Disease Taking Aspirin. Circulation 1995(92):2432-6.
32. Benowitz NL. Cigarette smoking and cardiovascular disease: Pathophysiology and implications for treatment. Prog Cardiovasc Dis. 2003(46):91-111.
33. Milionis HJ, Rizos E, Mikhailidis DP. Smoking diminishes the beneficial effect of statins: observations from the landmark trials. Angiology. 2001(52):575–87.
34. Journath G, Nilsson PM, Petersson U, Paradis BA, et al. Hypertensive smokers have a worse cardiovascular risk profile than non-smokers in spite of treatment: a national study in Sweden. Blood Pressure. 2005(14):144–50.
35. Frey P, Waters DD, DeMicco DA, Breazna A, Samuels L, et al. Impact of Smoking on Cardiovascular Events in Patients With Coronary Disease Receiving Contemporary Medical Therapy (from the Treating to New Targets [TNT] and the Incremental Decrease in End Points Through Aggressive Lipid Lowering [IDEAL] Trials). Am J Cardiol. 2011(107):145-50.
36. McEvoy JW, Blaha MJ, DeFilippis AP, et al. Cigarette Smoking and Cardiovascular Events. Role of Inflammation and Subclinical Atherosclerosis. From the Multiethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2015;35(3):700-9.
37. Schane R, Ling PM, Glanz S. Health Effects of Light and Intermittent Smoking : A Review. 2010(121):1518-22.
38. U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health,; 2014.
39. Buttar HS, Li T, Ravi N. Prevention of cardiovascular diseases: Role of exercise,

dietary interventions, obesity and smoking cessation. Exp Clin Cardiol. 2005;4(10):229-49.
40. Rose JE, Behm FM, Westman EC, Coleman RE. Arterial nicotine kinetics during cigarette smoking and intravenous nicotine administration: implications for addiction. Drug and alcohol dependence. 1999;2(56):99-107.
41. Lunell E, Molander L, Ekberg K, Wahren J. Site of nicotine absorption from a vapour inhaler–comparison with cigarette smoking. Eur J Clin Pharmacol. 2000;10(55):737–41.
42. Gourlay SG, Benowitz NL. Arteriovenous differences in plasma concentration of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine. Clin Pharmacol Ther 1997;4(62):453-63.
43. Benowitz NL, Hukkanen J, Jacob III P. Nicotine Chemistry, Metabolism, Kinetics and Biomarkers. Handb Exp Pharmacol. 2009(192):29-60.
44. Kuwabara H, Heishman SJ, Brasic J, C C, et al. Mu Opioid Receptor Binding Correlates with Nicotine Dependence and Reward in Smokers PLoS ONE 2014;12(9):e113694.
45. Pipe AL, Papadakis S, Reid RD. The role of smoking cessation in the prevention of coronary artery disease. Curr Atheroscler Rep 2010;12:145-50.
46. Ambrose J, Barua R. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004;10(43):1731-7.
47. Talhout R, Schulz T, Florek E, van Benthem J, et al. Hazardous compounds in tobacco smoke. Int J Environ Res Public Health 2011;2(8):613–28.
48. Polichetti G, Cocco S, Spinali A, Trimarco V, Nunziata A. Effects of particulate matter (PM(10), PM(2.5) and PM(1) on the cardiovascular system. Toxicology. 2009;1-2(261):1–8.
49. Rajat SB. Mechanisms of Coronary Thrombosis in Cigarette Smoke Exposure. Arterioscler Thromb Vasc Biol. 2013;7(33):1460-7.
50. Kaptoge S, Di Angelantonio E, Lowe G, et al. Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010(375):132–40.
51. U.S. Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.

REFERENCES

52. Raupach T, Schafer K, Konstantinides S, Andreas S. Secondhand smoke as an acute threat for the cardiovascular system: a change in paradigm. European heart journal. 2006(27):386–92.
53. He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton PK. Passive smoking and the risk of coronary heart disease—a meta-analysis of epidemiologic studies. N Engl J Med. 1999(340):920–6.
54. Repace J. Tobacco Smoke Pollution. In: Orleans CT, Slade J, Editors. Nicotine Addiction: Principles And Management. New York: Oxford University Press. 1993.
55. Barnoya J, Glantz SA. Cardiovascular effects of secondhand smoke: nearly as large as smoking. . Circulation. 2005;111(20):2684-98.
56. Oberg M, Jaakkola MS, Woodward A, et al. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet. 2011;377:139–46.
57. Aronow WS. Effect Of Passive Smoking On Angina Pectoris. . N Engl J Med. 1978;299:(21-4).
58. Heiss C, Amabile N, Lee AC, et al. Brief Secondhand Smoke Exposure Depresses Endothelial Progenitor Cells Activity And Endothelial Function. J Am Coll Cardiol 2008;51(18):1760-71.
59. Glantz SA, Parmley WW. Passive smoking and heart disease. Epidemiology, physiology, and biochemistry. Circulation 1991;83:1-12. 29;83(1):1-12.
60. Peinemann F, Moebus S, Dragano N, et al. Secondhand smoke exposure and coronary artery calcification among nonsmoking participants of a population-based cohort. Environ Health Perspect. 2011;119:1556-61.
61. Flouris AD, Vardavas CI, Metsios GS, Tsatsakis AM, Koutedakis Y. Biological Evidence For The Acute Health Effects Of Secondhand Smoke Exposure. Am J Physiol Lung Cell Mol Physiol 2010;298(3-13).
62. Whincup PH, Gilg JA, Emberson JR, et al. Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. BMJ. 2004;329(7459):200–5.
63. Teo KK, Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. Lancet. 2006;368(9536):647-58.
64. Frazer K, Callinan JE, McHugh J, et al. Legislative smoking bans for reducing harms from secondhand smoke exposure, smoking prevalence and tobacco consumption. Cochrane Database of Systematic Reviews. Cochrane Database Systematic Reviews 2016;CD005992(2).
65. Lightwood JM, Glantz SA. Declines in acute myocardial infarction after smoke-free laws and individual risk attributable to secondhand smoke. . Circulation. 2009;120(14):1373–9.

66. Dinno A, Glantz S. Clean indoor air laws immediately reduce heart attacks. Preventive Medicine. 2007;45(1):9-11.
67. Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. Arch Intern Med 2000;160(7):939-44.
68. Wannamethee SG, Tchernova J, Whincup P, et al. Plasma leptin: associations with metabolic, inflammatory and haemostatic risk factors for cardiovascular disease. Atherosclerosis. 2007;191(2):418–26.
69. Tuomisto K, Jousilahti P, Sundvall J, et al. C-reactive protein,interleukin-6 and tumor necrosis factor as predictors of incident coronary and cardiovascular events and total mortality: a population-based, prospective study. Thromb Haemost. 2006;95(3):511–8.
70. Pai JK, Pischon T, Ma J, al. e. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 2004;351(25):2599–610.
71. Demerath E, Towne B, Blangero J, et al. The relationship of soluble ICAM-1, VCAM-1, P-selectin and E-selectin to cardiovascular disease risk factors in healthy men and women. Ann Hum Biol. 2001;28(6):664–78.
72. Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). Am J Cardiol 2003;92(5):522–8.
73. Rasmussen T, Frestad D, Køber L, Pedersen JH, et al. Development and progression of coronary artery calcification in long-term smokers: adverse effects of continued smoking. J Am Coll Cardiol 2013;62(3):255–7.
74. Kronmal RA, McClelland RL, Detrano R, Shea S, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2007;115(21):2722–30.
75. Wannamethee SG, Lowe GD, Shaper AG, Rumley A, et al. Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. European heart journal. 2005;26(17):1765–73.
76. McEvoy JW, Nasir K, DeFilippis AP, Lima JA, et al. Relationship of Cigarette Smoking With Inflammation and Subclinical Vascular Disease.The Multi-Ethnic Study of Atherosclerosis. . Arterioscler Thromb Vasc Biol. 2015;35(4):1002-10.
77. Simon A, Megnien JL, Chironi G. The value of carotid intima-media thickness for predicting cardiovascular risk. Arterioscler Thromb Vasc Biol. 2010;30(2):182-5.
78. Prati P, Tosetto A, Vanuzzo D, et al. Carotid intima media thickness and plaques can predict the occurrence of

REFERENCES

ischemic cerebrovascular events. . Stroke 2008;39(9):2470–6.

79. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. Circulation. 2007;115(4):459-67.
80. Jiang F, Wang J, Zhang R, Chen M, et al. Effects of active and passive smoking on the development of cardiovascular disease as assessed by a carotid intima-media thickness examination in patients with type 2 diabetes mellitus. Clin Exp Pharmacol Physiol. 2015;42(5):444-50.
81. Reichert V, Xue X, Bartscherer D, Jacobsen D, Fardellone C, et al. A Pilot Study To Examine the Effects of Smoking Cessation on Serum Markers of Inflammation in Women at Risk for Cardiovascular Disease. Chest. 2009;136(1):212-9.
82. Woolf SH. The need for perspective in evidence-based medicine. JAMA. 1999;282(24):2356-65.
83. Lightwood J. The economics of smoking and cardiovascular disease. Prog Cardiovasc Dis. 2003;46(1):39-78.
84. Eddy DM. David Eddy ranks the tests. Harv Health Lett. 1992;17:10-1.
85. Kahn R, Robertson JT, Smith R, Eddy D. The Impact of Prevention on Reducing the Burden of Cardiovascular Disease. Circulation. 2008;118:576-85.
86. Haustein KO, Krause J, Haustein H, Rasmussen T, Cort N. Changes in hemorheological and biochemical parameters following short-term and long-term smoking cessation induced by nicotine replacement therapy (NRT). Int J Clin Pharmacol Ther. 2004;42(2):83-92.
87. van Domburg RT, Meeter K, van Berkel DFM, Veldkamp RF, van Herwerden LA, Bogers AJJC. Smoking cessation reduces mortality after coronary artery bypass surgery: a 20-year follow-up study. J Am Coll Cardiol. 2000;36(3):878-83.
88. U.S. Department of Health and Human Services. The Health Benefits of Smoking Cessation A Report of the Surgeon General. Atlanta: US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1990.
89. Barth J, Jacob T, Daha I, Critchley JA. Psychosocial interventions for smoking cessation in patients with coronary heart disease. Cochrane Database Syst Rev. 2015(7):CD006886.
90. Mohiuddin SM1, Mooss AN, Hunter CB, Grollmes TL, Cloutier DA, Hilleman DE. Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease. Chest.

2007;131(2):446-52.
91. Tonstad S, J. AJ. Cardiovascular risks associated with smoking: a review for clinicians. Eur J Cardiovasc Prev Rehabil. 2006;13(4):507-14.
92. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA. 2003;290(1):86-97.
93. Suskin N, Sheth T, Negassa A, Yusuf S. Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. J Am Coll Cardiol 2001;37(6):1677-82.
94. Suskin N, Pipe A, Prior P. Smokers paradox or not in heart failure. Just quit. European heart journal. 2008;29(16):1932-3.
95. Brilakis ES, Hernandez AF, Dai D, Peterson ED. Quality of care for acute coronary syndrome patients with known atherosclerotic disease: results from the Get With the Guidelines Program. Circulation. 2009;120(7):560-7.
96. Editorial. Cardiologists should be less passive about smoking cessation. The Lancet. 2009;373:867.
97. Kotseva K, Wood D, De Backer G, et al. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. Eur J Cardiovasc Prev Rehabil. 2009;16(2):121-37.
98. Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: US Dept of Health and Human Services, Public Health Service; 2008.
99. Forrester J.S., Bairey Merz C.N., Bush T.L., et al. Task Force 4. Efficacy of Risk Factor Management JACC. 1996;27(5):991-1006.
100. Hammal F, Ezekowitz JA, Norris CM, Wild TC, Finegan BA, APPROACH Investigators. Smoking status and survival: impact on mortality of continuing to smoke one year after the angiographic diagnosis of coronary artery disease, a prospective cohort study. BMC Cardiovasc Disord. 2014;14:133.
101. Pipe AL, Eisenberg MJ, Gupta A, Reid RD, Suskin NG, Stone JA. Smoking cessation and the cardiovascular specialist: Canadian Cardiovascular Society position paper. Can J Cardiol. 2011;27(2):132-7.
102. Rea TD, Heckbert SR, Kaplan RC, Smith NL, Lemaitre RN, Psaty BM. Smoking status and risk for recurrent coronary events after myocardial infarction. Ann Intern Med. 2002;137(6):494-500.
103. Rigotti NA, McKool KM, Shiffman S. Predictors of smoking cessation after coronary artery bypass graft surgery. Results of a randomized trial with 5-year follow-up. Ann Intern Med. 1994;120(4):287-93.
104. Reid RD, Mullen KA, Slovinec D'Angelo ME, et al. Smoking cessation for hospitalized

REFERENCES

smokers: an evaluation of the "Ottawa Model". Nicotine Tob Res. 2010;12(1):11-8.

105. Reid RD, Pipe AL, Quinlan B. Promoting smoking cessation during hospitalization for coronary artery disease. Can J Cardiol. 2006;22(9):775-80.
106. European Network for Smoking and Tobacco Prevention aisbl (ENSP). European Smoking Cessation Guidelines: The authoritative guide to a comprehensive understanding of the implications and implementation of treatments and strategies to treat tobacco dependence. First Edition; 2012.
107. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985;14(1):32-8.
108. Manuel DG, Lim J, Tanuseputro P, et al. Revisiting Rose: strategies for reducing coronary heart disease. BMJ. 2006;332(7542):659-62.
109. Stead LF, Buitrago D, Preciado N, Sanchez G, Hartmann-Boyce J, Lancaster T. Physician advice for smoking cessation. Cochrane Database Syst Rev. 2013(5):CD000165.
110. National Institute for Health and Clinical Excellence (NICE). Smoking cessation services in primary care, pharmacies, local authorities and workplaces, particularly for manual working groups, pregnant women and hard to reach communities. London; 2008.
111. Stead LF, Koilpillai P, Lancaster T. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. Cochrane Database Syst Rev. 2015(10):CD009670.
112. Mottillo S, Filion KB, Bélisle P, et al. Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. European heart journal. 2009;30(6):718-30.
113. Thomson CC, Rigotti NA. Hospital and clinic-based smoking cessation interventions for smokers with cardiovascular disease. Prog Cardiovasc Dis. 2003;45(6):459-79.
114. Dornelas EA, Sampson RA, Gray JF, Waters D, Thompson PD. A randomized controlled trial of smoking cessation counseling after myocardial infarction. Prev Med. 2000;30(4):261-8.
115. DeBusk RF, Miller NH, Superko R, et al. A case-management system for coronary risk factor modification after acute myocardial infarction. Ann Intern Med. 1994;120(9):721-9.
116. Lancaster T, Stead LF. Individual behavioral counseling for smoking cessation. The Cochrane Library Oxford: Update Software. 2005(3).
117. Stead LF, Lancaster T. Group behavior therapy programs for smoking cessation. The Cochrane Library, Issue 4 Oxford: Update Software. 2005;54.
118. Lichtenstein E, Glasgow RE, Lando HA, Ossip Klein DJ, Boles SM. Telephone counseling

for smoking cessation—rationales and meta-analytic review of evidence. Health Educ Res 1996;11:243–57.
119. Hartmann-Boyce J, Stead LF, Cahill K, Lancaster T. Efficacy of interventions to combat tobacco addiction: Cochrane update of 2012 reviews. Addiction. 2013;108(10):1711-21.
120. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;5:CD009329.
121. Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ. Cardiovascular Events Associated With Smoking Cessation Pharmacotherapies. A Network Meta-Analysis. Circulation. 2014;129:28-41.
122. Eisenberg MJ, Filion KB, Yavin D, et al. Pharmacotherapies for smoking cessation: a meta-analysis of randomized controlled trials. CMAJ 2008;179:135-44.
123. Woolf KJ, Zabad MN, Post JM, McNitt S. Effect of Nicotine Replacement Therapy on Cardiovascular Outcomes After Acute Coronary Syndromes. Am J Cardiol 2012;110:968-70.
124. Centers for Disease Control and Prevention. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US); 2010.
125 Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J Am Coll Cardiol. 1997;29(7):1422-31.
126. Mahmarian JJ, Moyé LA, Nasser GA, et al. Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischemia. J Am Coll Cardiol. 1997;30(1):125-30.
127. Nitenberg A, Antony I. Effects of nicotine gum on coronary vasomotor responses during sympathetic stimulation in patients with coronary artery stenosis. J Cardiovasc Pharmacol. 1999;34(5):694-9.
128. Working Group for the Study of Transdermal Nicotine in Patients with Coronary artery disease. Nicotine replacement therapy for patients with coronary artery disease. Arch Intern Med. 1991;154(9):989-95.
129. Joseph AM, Norman SM, Ferry LH, et al. The Safety of Transdermal Nicotine as an Aid to Smoking Cessation in Patients with Cardiac Disease. N Engl J Med. 1996;335:1792-8.
130. Hubbard R, Lewis S, Smith C, et al. Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. Tob Control. 2005;14(6):416-21.
131. Nicotine replacement therapy for patients

REFERENCES

with coronary artery disease. Working Group for the Study of Transdermal Nicotine in Patients with Coronary artery disease. Arch Intern Med. 1994;154(9):989-95.

132. Frishman WH, Ky T, Ismail A. Tobacco smoking, nicotine, and nicotine and non-nicotine replacement therapies. Heart Dis. 2001;3(6):365-77.
133. Haustein KO, Krause J, Haustein H, Rasmussen T, Cort N. Effects of cigarette smoking or nicotine replacement on cardiovascular risk factors and parameters of haemorheology. J Intern Med. 2002;252(2):130-9.
134. McRobbie H, Hajek P. Nicotine replacement therapy in patients with cardiovascular disease: guidelines for health professionals. Addiction. 2001;96(11):1547-51.
135. Meine TJ, Patel MR, Washam JB, Pappas PA, Jollis JG. Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. Am J Cardiol. 2005;95(8):976-8.
136. Stahl SM, Pradko JF, Haight BR, Modell JG, Rockett CB, S. L-C. A Review of the Neuropharmacology of Bupropion, a Dual Norepinephrine and Dopamine Reuptake Inhibitor. Prim Care Companion J Clin Psychiatry. 2004;6(4):159-66.
137. Mansvelder HD, Fagen ZM, Chang B, Mitchum R, et al. Bupropion inhibits the cellular effects of nicotine in the ventral tegmental area. Biochem Pharmacol. 2007;74(8):1283–91.
138. Lembke A, Johnson K, DeBattista C. Depression and smoking cessation: Does the evidence support psychiatric practice? Neuropsychiatr Dis Treat. 2007;3(4):487-93.
139. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2014;1:CD000031.
140. Joseph AM, Fu SS. Safety issues in pharmacotherapy for smoking in patients with cardiovascular disease. Prog Cardiovasc Dis. 2003;45(6):429-41.
141. Issa JS, Perez GH, Diament J, Zavattieri AG, de Oliveira KU. Effectiveness of sustained-release bupropion in the treatment of smoker patients with cardiovascular disease. Arq Bras Cardiol. 2007;88(4):434-40.
142. Tonstad S, Farsang C, Klaene G, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. European heart journal. 2003;24(10):946-55.
143. Eisenberg MJ, Grandi SM, Gervais A, et al. Bupropion for smoking cessation in patients hospitalized with acute myocardial infarction: A randomized, placebo-controlled trial. J Am Coll Cardiol. 2013;61(5):524-32.
144. Rigotti NA, Thorndike AN, Regan S, et al. Bupropion for smokers hospitalized with acute cardiovascular disease. Am J Med.

2006;119(12):1080-7.
145. Roose SP, Dalack GW, Glassman AH, Woodring S, Walsh BT, Giardina EG. Cardiovascular effects of bupropion in depressed patients with heart disease. Am J Psychiatry. 1991;148(4):512-16.
146. Roose SP. Considerations for the use of antidepressants in patients with cardiovascular disease. Am Heart J. 2000;140(4 Suppl):84-8.
147. Stefanatou A. Smoking Cessation in Cardiovascular Patients. Hellenic J Cardiol 2008;49(6):422-31.
148. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006;296(1):56-63.
149. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD006103. DOI: 10.1002/14651858.CD006103.pub7.
150. Aubin HJ, Bobak A, Britton JR, et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomized open-label trial. Thorax. 2008;63(8):717-24.
151. Ebbert JO, Wyatt KD, Hays JT, Klee EW, Hurt RD. Varenicline for smoking cessation: efficacy, safety, and treatment recommendations. Patient Prefer Adherence. 2010;4:355-62.
152. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation. 2010;121(2):221-9.
153. Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. CMAJ. 2011;183(12):1359-66.
154. Woods DJ, Caswell MD. Varenicline: quantifying the risk. CMAJ. 2011;183(12):1404.
155. Takagi H, Umemoto T. Varenicline: quantifying the risk. CMAJ. 2011;183(12):1404.
156. Squire EN. Varenicline: quantifying the risk. CMAJ 2011;183(12):1404-5.
157. Samuels L. Varenicline: quantifying the risk. CMAJ 2011;183(12):1407-8.
158. JT H. Varenicline for smoking cessation: is it a heartbreaker? CMAJ. 2011;183(12):1346-7.
159. European Medicines Agency. European Medicines Agency confirms positive benefit-risk balance for Champix. 2011 [cited; Available from: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/07/news_detail_001314.jsp&murl=menus/news_and_events/news_

REFERENCES

and_events.jsp&mid=WC0b01ac058004d5c1&jsenabled=true

160. Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation:systematic review and meta-analysis. BMJ. 2012;344:1-11.
161. Hughes JR. Motivating and Helping Smokers to Stop Smoking. J Gen Intern Med. 2003;18(12):1053-57.
162. Rigotti NA, Clair C, Munafo MR, Stead LF. Interventions for smoking cessation in hospitalised patients. Cochrane Database Syst Rev. 2012;16(5):CD001837.
163. Eisenberg MJ, Windle SB, Roy N, Old W, et al. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. Circulation. 2016; 133:21–30.
164. Mullen KA, Manuel DG, Hawken SJ, Pipe AL, et al. Effectiveness of a hospital-initiated smoking cessation programme: 2-year health and healthcare outcomes. Tobacco Control. 2016; 0;1-7.
165. Ezzati M, Henley J, Thun MJ, Lopez AD. Role of smoking in global and regional cardiovascular mortality. Circulation. 2005;112(4):489-7.
166. WB K. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA. 1996;275(20):1571-6.
167. Kannel WB, Higgins M. Smoking and hypertension as predictors of cardiovascular risk in population studies. J Hypertens. 1990;8(Suppl. 5):S3-S8.
168. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and differences by age for 316,099 white men. Arch Intern Med. 1992;152(1):56-64.
169. Rigotti NA, Pasternak RC. Cigarette smoking and coronary heart disease: risks and management. Cardiol Clin. 1996;14(1):51-68.
170. Mahmud A, Wadi H, Feely J, Silke B. Cigarette smoking reduces blood pressure response to antihypertensive treatment in newly diagnosed hypertensive patients. J Hypertens. 2015;33(Suppl 1):e94.
171 Wen CP, Tsai MK, Chan HT, Tsai SP, et al. Making hypertensive smokers motivated in quitting: developing 'blood pressure equivalence of smoking. J Hypertens. 2005;26(4):672-7.
172 Shahab L, Mindell J, Poulter NR, R. W. Hypertension and its identification among current, past and never smokers in an English population sample. Eur J Cardiovasc Prev Rehabil. 2010;17(1):63-70.
173 Agarwal S. The association of active and passive smoking with peripheral arterial disease: results from NHANES 1999-2004. Angiology. 2009;60(3):335-45.
174 Criqui MH. Peripheral arterial disease—epidemiological aspects. Vasc Med 2001;6(Suppl 1):3-7.

175 Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286(11):1317-24.

176 Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. Arch Intern Med 2003;163(16):1939-42.

177 Willigendael EM, Teijink JAW, Bartelink ML, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. J Vasc Surg 2004;40(6):1158-65.

178 Chi YW, Jaff MR. Optimal risk factor modification and medical management of the patient with peripheral arterial disease. Catheter Cardiovasc Interv. 2008;71(4):475-89.

179 Hennrikus D, Joseph AM, Lando HA, SueDuval, et al. Effectiveness of a Smoking Cessation Program for Peripheral Artery Disease Patients A Randomized Controlled Trial J Am Coll Cardiol. 2010;56(25):2105-12.

180 Lee Yh, Shin MH, Kweon SS, Choi JS, et al. Cumulative smoking exposure, duration of smoking cessation, and peripheral arterial disease in middle-aged and older Korean men. BMC Public Health. 2006;11(94):1-7.

181 Hobbs SD, Bradbury AW. Smoking Cessation Strategies in Patients with Peripheral Arterial Disease: An Evidence-based Approach. Eur J Vasc Endovasc Surg 2003;26(4):341–7

182 Samet JM, Young Yoon S. Women and the tobacco epidemic – challenges for the 21st century. World Health Organization (WHO). 2001.

183 Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ 1998;316(7137):1043-47.

184 Mucha L, Stephenson J, Morandi N, Dirani R. Meta-analysis of disease risk associated with smoking, by gender and intensity of smoking. Gend Med. 2006;3(4):279-91.

185 Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P 3rd. Female sex and oral contraceptive use accelerate nicotine metabolism. Clin Pharmacol Ther. 2006;79(5):480-8.

186 Prescott J, Ma H, Bernstein L, Ursin G. Cigarette smoking is not associated with breast cancer risk in young women. Cancer Epidemiol Biomarkers Prev. 2007;16(3):620-2.

187 Doolan DM, Froelicher ES. Smoking cessation interventions and older adults. Prog Cardiovasc Nurs 2008;23(3):119-27.

188 Mons U, Müezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. BMJ. 2015;350:h1551.

REFERENCES

189 Gellert C, Schöttker B, Müller H, Holleczek B, Brenner H. Impact of smoking and quitting on cardiovascular outcomes and risk advancement periods among older adults. Eur J Epidemiol. 2013;28(8):649-58.

190 Graham DJ, By K, McKean S, et al. Cardiovascular and mortality risks in older Medicare patients treated with varenicline or bupropion for smoking cessation: an observational cohort study. Pharmacoepidemiol Drug Saf. 2014;23(11):1205-12.

191 Bucholz EM, Beckman AL, Kiefe CI, Krumholz HM. Smoking status and life expectancy after acute myocardial infarction in the elderly. Heart (British Cardiac Society). 2016 Jan;102(2):133-9. ■

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