Smoking Prevention and Cessation in the Africa and Middle East Region: A Consensus Draft Guideline for Healthcare Providers – Full Text

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Glossary of terms

ACTH	adrenocorticotropic hormone
AMPS	All Media and Product Survey
ATCRI	Africa Tobacco Control Regional Initiative
BAT	British American Tobacco
CAD	coronary artery disease
CARs	continuous abstinence rates
CDC	Centers for Disease Control and Prevention
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CQRs	continuous quit rates
CVD	cardiovascular disease
EMA	European Medicines Agency
ETS	environmental tobacco smoke
FCTC	Framework Convention on Tobacco Control
FTCD	Fagerström Test for Cigarette Dependence
FTND	Fagerström Test for Nicotine Dependence
GYTS	Global Youth Tobacco Survey
ICD-10	International Classification of Diseases-10
IDRC	International Development Research Centre
IUATLD	International Union Against Tuberculosis and Lung Disease
LWDS-11	Lebanon Waterpipe Dependence Scale-11
MAO	monoamine oxidase
META	Middle East Tobacco Association
MEWG	Middle East Working Group
MI	Motivational Interviewing
n**ACh**R**s**	nicotinic acetylcholine receptor
NCAS	National Council Against Smoking
NHANES III	third National Health and Nutrition Examination Study
NICE	National Institute for Health and Clinical Excellence
NRT	Nicotine Replacement Therapy
OSH	Office on Smoking and Health
OTC	over the counter
PAHs	polyaromatic hydrocarbons
PCPs	primary care providers
RITC	Research for International Tobacco Control
SCTS	Syrian Centre for Tobacco Studies
SERT	serotonin transporter
SHS	second-hand smoke
SSRIs	selective serotonin reuptake inhibitors
TB	tuberculosis
TFI	Tobacco Free Initiative
TQD	target quit date
TSNAs	tobacco-specific nitroamines
TTCs	transnational tobacco companies
TTS	Tobacco Treatment Specialist
URTI	upper respiratory tract infection
VTA	ventral tegmental area
VOCs	volatile organic compounds
WHO	World Health Organization
WMH	World Mental Health
YRBS	Youth Risk Behavior Survey

Preface

About the authors

The authors of this document are a group of professionals, all working at public health services and/or academic institutions in Africa and the Middle East. We share a concern that many countries in our part of the world, the so called "developing" world, are struggling with the pandemic of tobacco addiction and its complications to a greater extent than the rest of the world [1]. In this undertaking, we represent ourselves as colleagues with a shared primary interest in treating tobacco dependence and specialist expertise in this area. Our smoking cessation guidelines for Africa and the Middle East are based on published evidence, review of overseas guidelines, and a process of iterative peer-review. The views expressed in these guidelines represent our personal judgment and we do not claim to represent the views of the institutions or organizations where we are employees.

Our group met for the first time in May 2008 in Cairo, Egypt, where the idea to develop a smoking cessation guideline document for Africa and the Middle East was first proposed. We were enthused by a similar effort by colleagues from Latin America, who published their guidelines and issued the Rio de Janeiro declaration in 2009 [2]. With the guidelines development under way, our group met again in Cape Town, South Africa (February 2009) and in Dubai, United Arab Emirates (June 2010), where representatives of the Latin American guidelines group were present. The shared insights from that group further strengthened our resolve to provide our colleagues in our countries with their own guidelines. In February 2011, we met in Dubai to consolidate and conclude the draft content. Over the course of the 2 years between our meetings, we exchanged information through regular phone calls and electronic communications. Through these discussions and face-to-face meetings, we reached a consensus of opinion which is represented in this document.

Is there a need for these guidelines?

We strongly feel that regional guidelines for smoking cessation are needed and that every effort should be made to tailor these to our part of the world in terms of epidemiological findings and the biopsychosocial interventions, bearing in mind the incredible diversity of cultures and fortunes of the countries involved.

Tobacco use spares no borders, age, gender or religion and kills a third to half of its users, with around 5 million tobacco-related deaths annually and a rising death toll, projected to reach up to 1 billion throughout the 21st century [1, 3].

Tobacco dependence diagnosed according to the International Classification of Diseases-10 (ICD-10) [4] is a chronic relapsing disease which is potentially treatable. The impact of interventions addressing its use, even brief interventions of 30 seconds, on public health outcomes is substantial and justifies investing in guidelines to encourage such actions.

Further, the WHO Framework Convention on Tobacco Control (FCTC), which was developed in response to the globalization of the tobacco epidemic in 2005, provides a comprehensive regulatory strategy to address tobacco addiction and asserts the importance of strategies to reduce both tobacco demand and supply [5]. Article 14 of the FCTC states that "each Party shall develop and disseminate appropriate, comprehensive and integrated guidelines based on scientific evidence and best practices, taking into account national circumstances and priorities, and shall take effective measures to promote cessation of tobacco use and adequate treatment for tobacco dependence". Hence, we see it as our role to respond to the need for guidelines and hope that our contribution will assist the parties involved in implementing these guidelines throughout Africa and the Middle East to combat the tobacco epidemic.

What are our intentions?

This effort aims to provide current and up-to-date best practice guidelines for all healthcare professionals and stakeholders involved in smoking cessation. The contents are intended to be user-friendly and to provide a reference guide for general practitioners, specialists and healthcare workers, community and non-governmental organizations, professional associations, and governments in the field.

The health effects of tobacco use (both smoked and smokeless) are addressed in the document. It is now well accepted that addiction to tobacco is a complex and chronic relapsing brain disease which leads to structural and biochemical changes in the brain leaving many individuals with a lifelong struggle to quit their tobacco habit, which is characterized by many attempts to quit and relapses. The reader should find the etiological factors and epidemiological data from the region, the neurobiology of tobacco addiction, and evidence-based pharmacological and non-pharmacological interventions, aligned with international guidelines.

What were our resolutions?

1. To seek publication of our guidelines in a peer-reviewed international journal to maximize reach and generate support

2. To adopt an approach in the guidelines inclusive of the concepts of prevention of smoking, promotion of tobacco cessation, as well as tobacco dependence treatment, as defined by the FCTC

3. To promote all efforts to increase awareness of the harm from tobacco use and prioritize youth and schools with such efforts

4. To advocate the broad accessibility to smoking cessation programs

5. To promote the training of doctors, nurses, paramedics and health workers and make available teaching materials for medical and other students

6. To promote and support the implementation of the FCTC

7. To emphasize the importance of integrated and comprehensive treatment programs in the treatment of tobacco addiction

8. To promote the use of simple tools of interventions for general practitioners, specialists and all health workers, e.g. the 5As, the 5Rs and the ABC, which have been proven to help in the efforts to quit

Chapter 1 Epidemiology of smoking in Africa and the Middle East

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Introduction

The World Health Organization (WHO) estimates that tobacco caused 5.4 million deaths in 2004 and that annual tobacco-attributable deaths will rise to 8.3 million by 2030, at which point these will represent almost 10% of all deaths globally [6]. By 2030, more than 80% of tobacco deaths will be in developing countries [3]. The scale of the epidemic and its growth is apparent in the contrast between the estimated death toll of 100 million for the 20th century and the current estimated death toll for the 21st century of 1 billion [3]. Nations least prepared to deal with the financial, social and political consequences of this global public health issue, including the countries of Africa and the Middle East region, will bear particularly high burdens [7].

As at 2000, 1.22 billion people worldwide were estimated to be tobacco users, and assuming a modest increase in income per capita this was predicted to reach 1.45 billion by 2010 and between 1.5 and 1.9 billion by 2025 [8]. Tobacco use is almost five times higher in men than women, and rates for women have begun to climb in developing countries [8].

Tobacco usage, in smoked and smokeless forms, occurs in all cultures worldwide [1]. Tobacco smoke contains more than 4,000 chemicals, more than 50 known or suspected carcinogens, and many potent irritants. Chemical carcinogens present in tobacco smoke include tobacco-specific nitrosamines (TSNAs), polyaromatic hydrocarbons (PAHs), and volatile organic compounds (VOCs) [1]. Carcinogenic nitrosamines are also present in smokeless tobacco products [9]. Despite the well-known adverse health effects of tobacco, people continue to use this, and once started, find it difficult to quit, due to addiction [10]. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine. Human and animal studies have shown that the powerful pharmacologic agent nicotine is the main psychoactive compound in tobacco that leads to addiction. The beta-carbolines harmane and norharmane which are present in cigarette smoke may also play a role in tobacco addiction by activating the firing and/or burst activity of dopamine neurons [11]. Smoking initiation and persistence are also influenced by genetic factors. Among the candidate genes predisposing to tobacco use are several genes involved in nicotine metabolism and dopamine catabolism, including genes encoding the nicotinic receptor, the dopamine D1, D2, D4 and D5 receptors, the serotonin transporter (SERT), dopamine beta-hydroxylase, and Cytochrome P450 [12–14].

Understanding the tobacco epidemic: the WHO/Lopez model

The WHO/Lopez model of the four stages of the evolving tobacco epidemic provides a conceptual framework to link the stages of the epidemic into a continuum, rather than a series of isolated events (Figure 1) [15]. This model, originally proposed by Lopez *et al*. [16], allows virtually any country to identify where it is in relation to the larger epidemic.

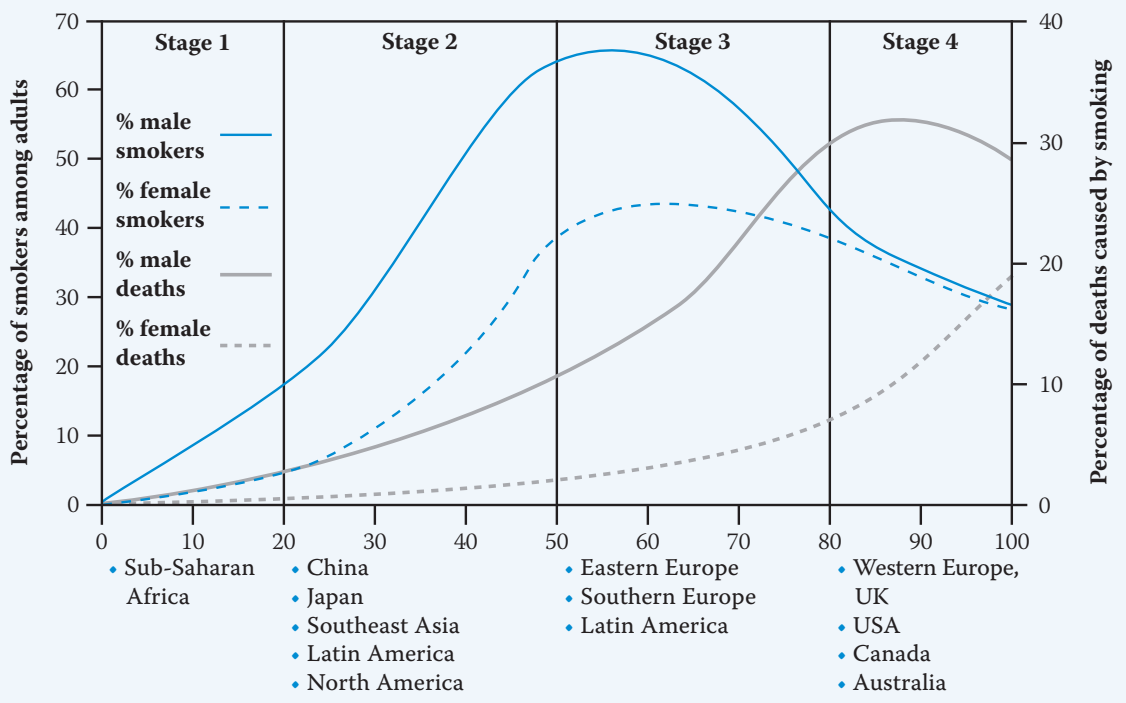

Figure 1: The four stages of the tobacco epidemic [15, 16]

- Stage 1: This is characterized by a low prevalence (<20%) of cigarette smoking, principally limited to males, and a prevalence among women of <10%, with as yet no apparent increase in lung cancer or other chronic diseases. Some Middle East and sub-Saharan African countries currently fit into this stage

- Stage 2: Prevalence rises to above 50% in men. Early increases in smoking are seen among women. There is a shift to smoking initiation at younger ages and an increasing burden of lung cancer and tobacco-related diseases in men. Many countries in Asia, North Africa, Latin America and the Middle East fit this profile, with low public and political support for implementation of effective tobacco control policies; and health risks of tobacco not well understood

- Stage 3: There is a discernible downturn in smoking prevalence among men and a more gradual decline in women, resulting in a convergence of male and female smoking prevalence. The burden of smoking-attributable disease and death continues to increase. At this stage, smoking-attributable deaths comprise 10–30% of all deaths and about three-quarters of these are in men (Eastern and Southern Europe). Health education decreases public acceptance of smoking

- Stage 4 is characterized by a further decline in smoking prevalence in men and women; death attributable to smoking among men peaks at 30–35% of all deaths (40–50% of deaths of middle-aged men) and subsequently declines. Smoking-attributable deaths rise to about 20–25% of all deaths in women. Industrialized countries in North and West Europe, North America and the Western Pacific are currently at this stage

The tobacco epidemic and its dimensions were further reviewed by Bolliger and Fagerström [17]. More recently, data from the first 17 countries participating in the WHO World Mental Health (WMH) Survey Initiative have been published [18]. These surveys, with a combined sample size of 85,052, were carried out between 2001 and 2005 in the Americas (Colombia, Mexico, USA), Europe (Belgium, France, Germany, Italy, the Netherlands, Spain, Ukraine), the Middle East and Africa (Israel, Lebanon, Nigeria, South Africa), Asia (Japan, the People's Republic of China), and Oceania (New Zealand). The results show that the estimated cumulative (lifetime) incidence of tobacco use is highest for the USA (74%), Mexico (60%), Ukraine (60%) and the Netherlands (58%); but lower for the African countries surveyed – South Africa (32%) and Nigeria (17%). Lebanon (67%) and Israel (48%) showed higher incidences than the African countries. By 15 years of age, the proportions of respondents who had initiated tobacco smoking were 44% for the USA; 18% for Lebanon; 15% for China; 21% for Mexico; 11% for South Africa; 9% for Israel; and 7% for Nigeria. Such cross-national epidemiological data, along with the WHO/Lopez model, provide valuable perspectives for monitoring the evolution of the smoking epidemic within countries and neighbouring regions.

Determinants of the tobacco epidemic

In the Middle East and African countries, as elsewhere, transnational tobacco companies (TTCs) which dominate the tobacco industry drive the tobacco epidemic through consumer-targeting operations and marketing strategies [19–21]. In the Middle East, TTCs formed the Middle East Working Group (MEWG) to co-ordinate their strategies. This group subsequently evolved into the Middle East Tobacco Association (META), while continuing to counter the efforts of Arab Gulf Health Ministers, National Tobacco Control coalitions, and the WHO Regional Headquarters in the Middle East [22]. In Africa, British American Tobacco (BAT) has strategically entrenched in countries across the continent [21, 23]. Regions and countries without strong control measures and surveillance thus remain vulnerable to the activities used by the TTCs and their cartels.

In countries where the economy is tied to tobacco farming and export earnings from tobacco, the tobacco industry often wields more influence. In Africa, the economies of Malawi and Zimbabwe are particularly dependent on tobacco exports – deriving 64% and 11%, respectively, of their export revenues from raw tobacco sales (2009 data for both) [24]. Furthermore, four African countries are among the global top 20 exporters of raw tobacco (values given are in US$ for 2009 exports): Malawi ($590M), Zimbabwe ($242M), Tanzania ($178M) and Mozambique ($107M), all neighboring countries in the south east of the continent [25].

Most adult smokers begin smoking during adolescence or early adulthood. Many factors may contribute to initiation of smoking and the WHO recently reviewed these (see Table 1) [26].

Personal Factors	**Sociodemographic factors,** e.g. age, gender, ethnicity and acculturation, family size and structure, and socioeconomic status.
	Socioeconomic factors, e.g. personal income, pricing of tobacco products, and psychosocial risk factors associated with socioeconomic status such as varying susceptibility to cigarette advertising.
	Knowledge, attitudes and beliefs, e.g. low knowledge of health risks, cultural beliefs, lack of systematic health-education programs, underestimating the magnitude of self-risk, and overestimating one's own ability to quit.
	Self-esteem, e.g. low self-esteem and low expectations for future achievement and smoking as a means of coping with the stress, anxiety, and depression associated with lack of self-confidence.
	Self-image, e.g. trying to create an external image of maturity or of being "cool", using smoking as a method to control appetite and weight, and seeking to emulate behavior of role models among peers or in the media.
Socio-environmental Factors	**Parental influence,** e.g. present or previous smoking by parents, including during pregnancy and parental attitudes to smoking.
	Peer tobacco use, e.g. influence of attitudes and behaviors of peers within social networks, including spouses, friends, and siblings, and the use of smoking as a shared activity with socializing functions.
	Marketing and advertising of tobacco products, e.g. direct and indirect advertising and promotion, exposure to other external cues, such as smoking in movies.

Table 1: Factors involved in initiation of tobacco use [26]

Maintenance of tobacco use results from tobacco addiction, lack of awareness of risk, and difficulty in quitting as a result of psychosocial and environmental factors, as well as dependence (Table 2).

Physiological Dependence	**Tobacco dependence.** This is recognized by the American Psychiatric Association and the WHO as a mental disorder. These organizations' definitions of dependence include a strong desire for a substance and difficulty controlling use; physiological withdrawal when use is stopped or reduced; evidence of tolerance; and persistent use despite knowledge of harms.
Psychosocial Factors	**Stress.** This can trigger smoking as a coping mechanism in both men and women. Women may be more vulnerable to smoking in response to emotional distress, such as anger, resentment, or anxiety.
	Depression. Cigarette smoking is more prevalent among individuals having psychiatric disorders such as schizophrenia, bipolar disorder, personality disorders, depression or panic disorders.
	Body weight. Concerns about weight may encourage smoking initiation, be a barrier to smoking cessation, and increase relapse rates after stopping smoking, particularly among women.
Temporal Factors	**Seasonal and circadian factors.** Smokers may smoke more in summer months, shortly after waking in the morning and shortly before going to sleep.

Table 2: Factors involved in maintenance of tobacco use [26]

In order to tackle the tobacco epidemic effectively in countries of Africa and the Middle East, understanding the role of the initiation- and maintenance-influencing factors mentioned above, along with any local genetic, racial and educational differences that drive the epidemic, is important.

Prevalence of smoking: a) The Middle East

The WHO data currently available for adult tobacco smoking in the Middle East countries are shown in Table 3. Note that the prevalence of smoking within males and females in a particular population is influenced by the age structure of that population. Within the tables in this chapter, the gender-specific prevalence for each country is shown as both crude rates (i.e. not adjusted to take account of the age structure of the population, for example a particularly high proportion of youth within a population) and age-standardized rates (i.e. the rate which is adjusted to take into consideration the age structure within a population). Age-standardization is useful when comparing prevalence data from different countries.

Between 1995 and 2000, cigarette consumption increased by 22.6% in the Eastern Mediterranean region [8], reflecting the high male smoking prevalence in the Arab world and the uptake of smoking by a rising number of women [27]. Some Arab countries – Djibouti, Yemen, Lebanon, Jordan, Egypt, Tunisia and Syria – have very high (>50%) adult male smoking prevalence rates, with Yemen and Djibouti in the range of 75% [1]. Tunisia and Egypt have the highest prevalence of daily tobacco smoking (50.3 and 39.2%, respectively). Age-standardized smoking prevalence in adults is highest in Jordan and Tunisia (36.5 and 25.7%, respectively), although such data are not available for Djibouti and Yemen [3].

Yemen (77.0%) and Djibouti (75.0%) had the highest prevalence of current smoking among adult males, followed closely by Lebanon (61.0%) and Jordan (50.5%). The prevalence of daily smoking in adult males ranged from 50.3% in Tunisia to 5.0% in Iraq [1].

Current tobacco smoking in female adults was most common in Lebanon (57.1%), Yemen (29.0%) and Djibouti (10.0%) [1].

	Daily Tobacco Smoking (crude %)		Current Tobacco Smoking (crude %)		Age-standardized adults smoking prevalence (%)
Country	Male	Female	Male	Female	
Bahrain (2001)	13.2	1.7	15.0	3.1	7.5
Djibouti (1999)	NA	NA	75.0	10.0	NA
Egypt (2005)	39.2	0.4	59.3	2.7	14.3
Iran (2005)	20.9	2.9	24.1	4.3	13.7
Iraq (2006)	5.0	4.1	41.5	6.9	5.8
Israel (2003)	13.9	9.1	NA	NA	21.3
Jordan (2002)	NA	NA	50.5	8.3	36.5
Kuwait (1996)	NA	NA	34.4	1.9	17.0
Lebanon (2002)	NA	NA	61.0	57.1	17.3
Libya (2003)	32.0	1.5	NA	NA	16.7
Morocco (2006)	30.3	0.2	NA	NA	14.2
Oman (2000)	NA	NA	13.4	0.5	5.7
Qatar (1999)	NA	NA	37.0	0.5	NA
S. Arabia (2006)	37.6	6.0	NA	NA	7.8
Sudan (1999)	-	-	23.5	1.5	NA
Syrian Arab Rep. (1999)	47.0	8.0	51.0	10.0	NA
Tunisia (2003)	50.3	1.9	52.1	2.0	25.7
UAE (2004)	17.6	1.4	28.1	2.4	7.6
West Bank/Gaza (1997)	-	-	40.7	3.2	NA
Yemen (1998)	-	-	77.0	29.0	NA

Notes: Tobacco smoking: Smoking any form of tobacco, including cigarettes, cigars, pipes, bidis, kreteks, etc.; Daily tobacco smoking: Smoking every day at the time of the survey; Current tobacco smoking: Smoking at the time of the survey, including daily and non-daily smoking; NA: No data available; Dates shown after each country reflect the date of local smoking surveys which the WHO used as data sources

Table 3: Prevalence Middle East countries [1]

Local considerations: waterpipe or hookah use

The use of a waterpipe, a centuries-old traditional method of tobacco use, also known as shisha, hubble bubble, sheesha, hookah, Jurak, qalyoun, argileh, narghile, and nargile, is a burgeoning trend in the Middle East, across North Africa and in many other countries globally. The practice comprises the passage of charcoal-heated air through perforated aluminium foil separating charcoal from flavored tobacco (also referred to as maassel). The heated air thus becomes a smoke, which cools as it bubbles through water, before inhalation by the smoker. Chewing of tobacco may also accompany waterpipe use. Observations in Jordan [28], Syria [29], Lebanon [30], Yemen [31], Saudi Arabia [32, 33], and Egypt [34] indicate that narghile smoking is prevalent throughout the region and is particularly common among high school students. Large numbers of young females are taking up this habit, which may be due to relative permissiveness of adult family members

towards waterpipe use, despite a strong taboo against female cigarette smoking [35].

Since the early 1990s, waterpipe use has been growing among youths and adults [36]. Among young people in Middle Eastern countries, the prevalence rates for current smokers (use within the past month) now ranges from 6–34% [37, 38] (*vs* 5–23% in American university students) [38–40]. Akl *et al.* performed a systematic review of the effects of waterpipe tobacco smoking on health outcomes [41]. This analysis used Cochrane Collaboration methodology to evaluate 24 identified studies. The authors concluded that waterpipe smoking is significantly associated with and doubles the risk of lung cancer, respiratory illness, low birth weight and periodontal disease. Waterpipe smoke contains many of the same toxicants as cigarette smoke, including those that cause cardiovascular disease (carbon monoxide), lung cancer (polycyclic aromatic hydrocarbons) and dependence (nicotine) [38]. As waterpipe smokers take deeper puffs and their smoking session is typically longer than the time it takes to smoke a cigarette, the waterpipe smoker may inhale as much smoke during a single session as a smoker would inhale consuming 100 or more cigarettes [42].

The Aleppo Household Survey conducted by the Syrian Centre for Tobacco Studies (SCTS) in 2004 showed that the prevalence of cigarette smoking among men and women was 56.9 and 17%, respectively, while the prevalence of waterpipe smoking was 20.2 and 4.8%, respectively. Interest in quitting was greater for cigarette than waterpipe smokers (74.0% *vs* 48.6%), while quit rates were higher for waterpipes compared to cigarettes (28.2% *vs* 16.5%) [43].

In Qatar (population 724,125), the Gulf Family Health Survey reported that 37% of males and 0.5% of females were smokers in 1999 [44].

Prevalence of smoking: b) Africa

The WHO data currently available for adult tobacco smoking in the African countries are shown in Table 4. Note that the prevalence of smoking within males and females in a particular population is influenced by the age structure of that population. Within the tables in this chapter, the gender-specific prevalence for each country is shown as both crude rates (i.e. not adjusted to take account of the age structure of the population, for example a particularly high proportion of youth within a population) and age-standardized rates (i.e. the rate which is adjusted to take into consideration the age structure within a population). Age standardization is useful when comparing prevalence data from different countries.

	Daily Tobacco Smoking (crude %)		Current Tobacco Smoking (crude %)		Age standardized adults smoking prevalence (%)
Country	Male	Female	Male	Female	
Algeria (2003)	32.3	0.4	38.1	0.5	14.4
Burkina Faso (2003)	19.0	10.3	23.6	11.1	14.7
Cameroon (2003)	-	-	-	-	6.0
Chad (2003)	13.2	2.1	17.4	2.9	7.4
Comoros (2003)	24.1	15.0	27.8	17.0	17.0
Congo (2003)	10.7	1.1	13.0	1.3	4.7
Cote d'Ivoire (2003)	14.5	1.2	19.3	2.3	6.7

Notes: Tobacco smoking: Smoking any form of tobacco, including cigarettes, cigars, pipes, bidis, kreteks, etc.; Daily tobacco smoking: Smoking every day at the time of the survey; Current tobacco smoking: Smoking at the time of the survey, including daily and non-daily smoking; NA: No data available; Dates shown reflect the date of national smoking surveys which the WHO used as data sources

Table 4: Prevalence African countries (cont. overleaf) [1, 3]

	Daily Tobacco Smoking (crude %)		Current Tobacco Smoking (crude %)		Age standardized adults smoking prevalence (%)
Country	Male	Female	Male	Female	
Congo (2005)	10.2	0.6	14.2	1.2	6.2
Eritrea (2004)	-	-	-	-	6.4
Ethiopia (2003)	5.3	0.4	6.3	0.5	2.8
Gambia (1997)	-	-	38.5	4.4	15.0
Ghana (2003)	6.2	0.4	9.0	1.2	4.0
Guinea (1998)	-	8.6	-	-	NA
Kenya (2004)	21.2	0.9	26.2	1.9	11.3
Lesotho (2001)	-	-	47.9	34.2	NA
Madagascar (2005)	-	-	-	-	NA
Malawi (2003)	20.6	5.1	25.5	6.1	12.0
Mali (2003)	18.8	1.6	24.1	2.3	9.0
Mauritania (2003)	23.2	3.2	27.4	4.2	10.8
Mauritius (2003)	32.2	1.1	42.5	2.9	14.8
Mozambique (2004)	-	-	-	-	9.4
Namibia (2003)	22.3	9.4	28.0	12.4	20.6
Niger (1991)	-	-	40.6	11.3	NA
Nigeria (1990)	-	-	-	-	15.4
Rwanda (2000)	-	-	-	-	NA
Sao Tome and Principe (1997)	-	-	-	-	15.6
Senegal (2003)	19.8	1.0	22.2	1.7	8.5
Seychelles (2004)	-	-	-	-	16.7
Sierra Leone (1999)	-	-	-	-	NA
South Africa (2002–2003)	27.1	8.2	36.0	10.2	14.2
Swaziland (2003)	9.9	2.1	13.8	3.3	5.9
Uganda (2000–2001)	-	-	25.2	3.3	9.3
Utd Rep. Tanzania (1998–1999)	-	-	-	-	11.5
Zambia (2003)	15.3	3.4	22.7	5.7	10.4
Zimbabwe (2005)	33.4	5.0	-	-	11.6

Notes: Tobacco smoking: Smoking any form of tobacco, including cigarettes, cigars, pipes, bidis, kreteks, etc.; Daily tobacco smoking: Smoking every day at the time of the survey; Current tobacco smoking: Smoking at the time of the survey, including daily and non-daily smoking; NA: No data available; Dates shown reflect the date of national smoking surveys which the WHO used as data sources

Table 4: Prevalence African countries (cont.) [1, 3]

Many sub-Saharan African countries are in the early stages of the tobacco epidemic (see Figure 1) and, with the exception of South Africa, tobacco consumption in Africa has increased faster than in the developing world as a whole in recent years, particularly among the young [15]. Cigarette consumption in the African region increased by 38.4% between 1995 and 2000 [8]. Smoking rates among youth outstripped adult rates, as transnational tobacco companies target African youths [15].

In adult males, prevalence of daily tobacco smoking ranged from 5.3% in Ethiopia to 33.4% in Zimbabwe. Lesotho (47.9%), Mauritius (42.5%), and Niger (40.6%) had the highest prevalence of current smoking in male adults [1, 3]. Countries which have prevalence of 20% and below, such as Chad, Democratic Republic of Congo, and Cote d'Ivoire, are in stage I of the tobacco epidemic, whereas several other countries such as Lesotho (47.9%), Mauritius (42.5%), and Niger (40.6%) appear to be making the transition to stage II of the WHO/Lopez epidemic model (characterized by smoking prevalence of ≥50% in men).

The WHO WMH Survey Initiative (2008) reported that lifetime tobacco use was lowest in South Africa (31.9%) and Nigeria (16.8%), while it was most common in USA (73.6%), Lebanon (67.4%), Mexico (60.2%), the Netherlands (58.0%), and Ukraine (60.6%) [18]. Studies in the Nigerian population suggest an increasing trend of tobacco use within the country. For example, a survey of 1,271 adult heads of Nigerian households in 1990 estimated that the overall prevalence of regular smoking was 22.6% [45]. More recently, a 2007 survey of 1,793 adults in Yola, north-east Nigeria, reported that 31.9% of respondents were current smokers [46].

Current and/or daily tobacco smoking amongst females in most of the African countries surveyed remains at levels consistent with stage I (<5%), except in Lesotho (34.2%), Comoros (17.0%), Namibia (12.4%), Niger (11.3%), and Burkina Faso (11.1%). The targeting of women as an untapped market in the African countries and other parts of the developing world by the tobacco industry is a relatively recent phenomenon. Themes of body image, fashion, and independence from cultural prohibitions feature prominently in these marketing strategies [47].

Co-ordinated initiatives against the tobacco epidemic in Africa include the Research for International Tobacco Control (RITC) program of the International Development Research Centre (IDRC) which was carried out in 12 sub-Saharan African countries – Burkina Faso, Cameroon, Eritrea, Ghana, Kenya, Malawi, Mauritius, Nigeria, Senegal, South Africa, Tanzania, and Zambia – to understand determinants for success against the tobacco epidemic [48]. The results (which are available from http://atsa.atcri.org/) will help efforts to build capacity for country-owned and country-driven control measures against tobacco.

Local considerations: tobacco production and availability

Despite the RITC program, many African countries are grappling with situation analyses of tobacco control. This may be particularly difficult in countries where tobacco is grown such as Malawi, Zimbabwe, Tanzania, Mozambique, Namibia, and Nigeria. Investments by tobacco companies in tobacco production may be seen by local political leaders as providing a short-term economic benefit, but such investments ultimately displace other, less destructive economic activities. Between 1970 and 2000, land hectares for tobacco utilization increased by more than 20% in Zimbabwe, Malawi, Tanzania, Ghana, Rwanda, Niger, Kenya, Mali, and Chad [15].

Smuggling cigarettes across national borders is widespread in Africa [23, 49]. Such smuggling undermines public health efforts to reduce tobacco use by making international brands more affordable to low-income consumers and to youth, thus stimulating consumption [1].

Consumption of smokeless tobacco, such as through nasal application of dried snuff, chewing of tobacco leaves or sucking of dried tobacco balls (known as toombak in Sudan), is common amongst adults and youths in many parts of Africa [50–53] Hand-rolled cigarettes are also popular and in South Africa account for about 21% of the tobacco market [54].

Smoking prevalence amongst health professionals

Smoking is a key issue in the medical profession as physicians play a leading role in efforts to prevent tobacco use within the community and are also involved in the development of overall policy. Surveys on the prevalence of smoking among health professionals in the countries of the Middle East and Africa are limited. Smith and Leggat performed an international comparison of tobacco smoking surveys conducted among physicians between 1974 and 2004 [55]. In the only African survey identified, 3% of the medical professional respondents in Nigeria were smokers (2002). In the Middle East, the prevalence estimates were: UAE 36% (1992); Kuwait 38% (1990); Saudi Arabia 34% (1987); Israel 16% (1996); and Iran 9% (2001). Another questionnaire-based study gathered information on smoking behavior from clinicians or epidemiologists involved in tobacco prevention in the Mediterranean countries of Europe, North Africa, and the Middle East [56]. Within each of the 10 participating countries, data were collated from conference abstracts, theses, national statistics, and/or unpublished observations. In most of the countries studied, the prevalence of smoking in doctors was estimated to be equal to or higher than that of the rest of the population. In Egypt (40%), Greece and Italy (40%), correspondents estimated that it was higher, while in Algeria (40%), Iran, and Tunisia it was believed to be similar. In only four regions was it believed to be below the rates in the general population: Catalonia (31%), Lebanon (38%), Morocco (30%), and Syria (30–35%).

The importance of smoking amongst health professionals as a factor influencing smoking behavior in Africa and Middle East countries needs to be emphasized as doctors incur a certain responsibility as exemplars for patients with regard to health behavior. If physicians themselves are smokers, this can lead to skepticism on the part of patients and undermine the message to smokers to quit.

Related to actual smoking by health professionals is the issue of education on tobacco in medical schools. In a worldwide survey of 493 medical schools in 93 countries (including the Middle East and Africa), 70% of institutes in developing countries indicated that "Lack of sufficient knowledge and training" was a problem which affected efforts to place the topic of tobacco and related diseases onto the medical curriculum [57]. Furthermore the survey showed that in the Middle East, 83% of the schools mentioned tobacco issues during medical training, but lacked a systematic approach to this topic. A notable finding for African (and Asian) training centers was that around a quarter of colleges (24%) did not include tobacco issues on their curriculum for medical training. The Tobacco Prevention Section of the International Union Against Tuberculosis and Lung Disease (IUATLD) has produced a book titled "Educating medical students about tobacco: planning and implementation" [58] – which should serve as template and tool for medical training centers in the Middle East and African countries.

Despite their future role in healthcare provision, many medical students are smokers. The IUATLD, in collaboration with the WHO, the American Cancer Society, and the International Union against Cancer, has conducted a series of studies in medical schools globally [59]. The surveys were conducted among more than 9,000 students from 51 medical schools in 42 countries including Africa and the Middle East. Across 10 African countries (Algeria, Egypt, Morocco, Tunisia, Benin, Kenya, Madagascar, Nairobi, Nigeria, and Senegal), on average 29% and 10% of male and female medical students were smokers, respectively. Smoking was also common in the Middle East countries examined: 27.5% and 2.3% of male and female students in Bahrain were smokers, as were 18.4% and 12.5% of male and female students in Israel. The gradual disappearance of smoking among physicians will be a welcome change in the social climate and will benefit smoking cessation programs in Africa and Middle East countries.

Passive smoking/environmental tobacco smoke

Passive smoking, also referred to as exposure to environmental tobacco smoke (ETS) or second-hand smoke (SHS), has serious health consequences. A retrospective analysis of data from 192 countries recently estimated the worldwide burden of disease from exposure to ETS [60]. The findings suggest that approximately 1% (603,000) of worldwide deaths were attributable to ETS in 2004. Worldwide, 40% of children, 33% of male non-smokers, and 35% of female non-smokers were exposed to ETS in 2004. It was estimated that 379,000 deaths from ischemic heart disease, 165,000 from lower respiratory infections, 36,900 from asthma, and 21,400 from lung cancer occurred as a result of this exposure. The largest disease burdens were from lower respiratory infections in young (<5 years old) children (5,939,000), ischemic heart disease in adults (2,836,000), and asthma in adults (1,246,000) and children (651,000) [60]. ETS exposure also increases the overall risk of cardiovascular and respiratory disease, lung cancer and other cancers, and ear infection and sudden infant death syndrome in children [61, 62]. The consensus from medical experts is that there is no safe form of tobacco and no safe level of exposure to SHS [1]. The term "thirdhand smoke" describes residual tobacco smoke contamination that remains after a cigarette is extinguished. Thirdhand smoke is a hazardous exposure resulting from cigarette smoke residue that accumulates in cars, homes, and other indoor spaces. Tobacco-derived toxins can react to form potent cancer causing compounds. Exposure to thirdhand smoke can continue to occur through the skin, by breathing, and by ingestion after smoke has cleared [63].

Table 5 shows the current data on youth exposure to ETS in the home for the Middle East and African countries for which data are available [1].

Middle East	%	Africa	%
Lebanon	78.9	Burkina Faso	35.7
Jordan	65.0	Niger	33.9
Yemen	44.0	Sudan	28.4
Mauritania	43.8	Zimbabwe	27.4
Iran	42.9	Swaziland	27.1
Libya	40.3	Benin	22.0
Egypt	38.0	Togo	20.2
Morocco	30.0	Ghana	18.1
UAE	26.5	Ethiopia	16.7
Oman	21.8		

Table 5: Youth exposed to ETS in the home [1]

Currently in the Middle East and Africa, regulations ensuring smoke-free environments in healthcare, educational and government facilities are being implemented as additional countries ratify the WHO FCTC. In 2008, the WHO reported that only 9% of high-income countries, 4% of middle-income countries, and 3% of low-income countries have implemented the highest level of smoke-free legislation (covering all institutions and places assessed). In 15% of high-income countries, 45% of middle-income countries and 31% of low-income countries, there is a complete absence of smoke-free legislation or weak legislation which fails to cover healthcare and educational institutions [3].

Global Youth Tobacco Survey

The Global Youth Tobacco Survey (GYTS) has been developed by the Tobacco Free Initiative (TFI) of the WHO, and the Office on Smoking and Health (OSH) of the Centers for Disease Control and Prevention (CDC) to provide standardized systematic global data on youth tobacco use [64]. This ongoing initiative helps countries to monitor tobacco use and thereby to meet the provisions of Article 20 of the WHO FCTC, which aims to establish research and surveillance of the magnitude, patterns, determinants and consequences of tobacco consumption. Since implementation began in 1999, GYTS has carried out school-based surveys of youths aged 13–15 years in 140 WHO member states. Follow-up surveys within many of these countries have also been completed and are under way or planned for the remainder.

The GYTS has detected changes in tobacco use among 13–15 year olds between 1999 and 2008 [65]. The results for the Middle East and African countries are summarized in Tables 6 and 7.

Comparison of the latest GYTS results with earlier GYTS results shows that current cigarette smoking decreased significantly for boys and girls in Burkina Faso, Mali, Niger, Zimbabwe, and Jordan; for boys in Oman, and girls in Somalia. Current smoking increased (although non-significantly) for boys and girls in Botswana and Syria; and for girls in Mauritania, the West Bank, and the UAE. There were no significant changes over time in the 12 remaining sites in Africa and 11 other sites in the Middle East studied [65].

Current Cigarette Smoking					Current use of other tobacco products		
Country	Years	Total %	Boys %	Girls %	Total %	Boys %	Girls %
Egypt	2001/2005	4.2/2.3	3.9/5.9	4.0/1.4	15.3/10.1	18.3/12.3	12.0/6.7
Gaza	2000/2005	9.0/6.6	15.1/9.7	3.4/3.0	7.8/11.7	12.4/12.8	3.6/10.0
Iran	2003/2007	2.0/3.0	3.2/5.1	1.0/0.9	12.1/26.1	16.0/31.9	8.7/19.5
Jordan	1999/2003/2007	16.6/17.7/10.3	22.0/21.4/32.2	9.9/12.6/7.1	11.2./20.0/26.4	14.5/21.4/28.2	7.1/18.2/23.5
Kuwait	2001/2005	10.0/10.8	14.8/17.7	4.9/4.5	16.2/14.5	19.1/17.4	12.9/11.7
Lebanon	2001/2005	7.5/8.6	10.4/11.8	5.3/5.6	38.6/40.0	45.0/44.7	33.9/35.7
Libya	2003/2007	4.1/4.6	7.3/7.7	0.8/0.9	9.8/7.2	11.7/8.6	7.5/5.6
Morocco	2001/2006	2.6/3.5	3.9/4.3	1.0/2.1	9.2/9.0	10.4/10.3	7.6/6.9
Oman	2002/2007	6.8/2.3	14.2/3.5	1.8/1.2	9.4/5.7	14.0/7.1	6.4/3.3
Qatar	2004/2006	6.4/6.5	10.7/13.4	2.8/2.3	13.7/15.6	15.9/19.4	12.0/12.6
Somalia	2004/2007	18.6/5.8	8.6/4.9	14.8/4.5	18.7/12.5	15.0/12.7	15.0/9.8
Sudan	2001/2005	6.1/6.0	10.8/10.2	1.9/2.1	13.5/10.2	17.2/11.0	10.4/9.3
Syria	2002/2007	6.3/12.3	8.1/19.1	3.1/5.9	17.6/22.6	19.2/29.7	14.5/15.3
Tunisia	2001/2007	10.1/8.3	17.6/15.1	3.0/1.6	7.2/13.9	11.3/19.9	3.1/7.8
UAE	2002/2005	6.8/8.0	11.7/12.1	2.2/3.6	15.0/28.8	19.0/32.7	10.2/24.7
West Bank	2003/2008	14.2/18.0	24.7/27.6	4.7/8.7	14.6/12.4	23.7/20.8	10.0/12.7
Yemen	2003/2008	5.3/3.9	6.5/4.2	3.0/1.6	15.7/12.1	15.7/12.1	12.1/10.1

Table 6: Middle East: Tobacco use among 13–15 year olds (GYTS, 1999–2008) [65]

Current Cigarette Smoking					Current use of other tobacco products		
Country	Years	Total %	Boys %	Girls %	Total %	Boys %	Girls %
Botswana	2001/2008	8.3/14.3	10.4/18.1	6.5/10.9	9.5/15.2	10.0/16.3	9.1/14.3
B/Faso	2001/2006	19.0/8.4	26.1/14.1	11.6/2.4	6.9/7.2	7.9/9.3	6.3/4.8
Ghana	2000/2006	4.2/2.7	5.0/2.8	3.1/2.3	14.6/10.4	13.6/10.1	15.5/10.1
Kenya	2001/2007	6.6/8.2	8.7/11.2	4.7/5.2	8.9/10.1	9.0/8.2	8.9/11.4
Lesotho	2002/2008	9.2/10.1	16.6/11.8	4.8/7.5	14.8/19.5	12.3/20.4	14.8/17.9
Malawi	2000/2005	2.4/1.7	4.2/2.0	0.9/1.4	14.7/8.6	14.4/8.8	15.2/8.3
Mali	2001/2008	23.5/9.5	41.8/18.6	4.6/1.7	9.1/9.1	13.1/14.8	4.8/4.2
Mauritania	2001/2006	14.8/19.5	19.8/20.3	8.8/18.3	14.9/18.0	15.8/18.4	13.4/17.3
Mauritius	2003/2008	13.2/13.7	19.8/20.3	7.7/7.7	NA	NA	NA
Mozambique	2002/2007	3.1/2.7	5.0/4.5	1.4/1.2	5.8/8.2	5.4/9.6	6.0/6.8
Niger	2001/2006	14.8/6.3	22.4/11.7	6.1/1.1	7.6/6.6	6.7/6.1	7.5/7.0
Nigeria	2000/2008	7.0/4.1	7.7/6.8	3.3/1.2	14.0/23.3	18.6/23.9	9.4/17.5
Senegal	2002/2007	13.2/7.5	20.2/12.1	4.4/2.7	5.4/9.3	7.3/11.7	2.9/7.7
Seychelles	2002/2007	26.8/21.5	29.9/23.2	23.9/20.0	9.3/10.5	13.0/10.6	5.5/9.2
South Africa	1999/2002	17.6/14.8	20.0/21.0	15.3/10.6	11.8/13.1	15.7/14.8	9.4/11.9
Swaziland	2001/2005	6.4/5.6	10.4/8.9	3.4/3.2	6.8/7.5	8.9/8.5	5.2/6.9
Togo	2002/2007	11.0/6.2	14.9/9.1	4.0/1.7	8.7/10.4	9.5/12.1	7.1/7.4
Uganda	2002/2007	3.2/5.2	3.7/5.7	2.6/4.2	9.7/13.3	9.7/14.3	9.8/12.0
Zambia	2002/2007	9.2/6.8	9.4/6.7	8.7/6.8	17.7/22.8	17.1/22.8	17.3/22.8
Zimbabwe	1999/2003 /2008	10.7/4.1/ 3.2	11.6/6.1/ 4.8	9.9/3.2/ 1.5	9.5/6.6/ 9.6	11.0/8.4/ 10.9	8.4/4.8/ 7.5

Table 7: Africa: Tobacco use among 13–15 year olds (GYTS, 1999–2008) [65]

The use of other tobacco products increased significantly for boys and girls in Iran, Jordan, Tunisia, the UAE, and Botswana. This also increased significantly for boys in Syria, Lesotho, Mozambique, and Senegal. It increased significantly for girls in the Gaza Strip. Use of other tobacco products decreased significantly for boys and girls in Malawi, Egypt, and Oman; and for boys in Sudan [65]. Overall, around one third of countries showed an increased use of other tobacco products, which is likely to be linked to increased use of waterpipes and smokeless tobacco products among the young (and which, as discussed earlier, have particular relevance for the countries of the Middle East and Africa). The GYTS findings support the conclusion of the WHO report on the global tobacco epidemic: "Member states have a long way to go before they are effectively protecting their citizens from the Tobacco epidemic" [3].

Mortality

By 2030, the WHO forecasts that more than 8 million people will die a year of smoking-related illness and that the tobacco epidemic could kill up to 1 billion people in the 21st century – a 10-fold rise over the 100 million who died in the 20th century [3]. About half of all persistent cigarette smokers are killed by their habit – a quarter while still in middle age (35–69 years) [66].

Tobacco users die on average 10–15 years prematurely and most smokers would like to quit, but are unable to because of dependence [3, 66].

A review of global smoking-attributable mortality for 2000 found that the leading causes of death from smoking in the developing world were cardiovascular diseases (0.67 million deaths), chronic obstructive pulmonary disease (COPD) (0.65 million deaths), and lung cancer (0.33 million deaths) [67]. In general, there was wider variation in the mortality caused by smoking among countries of the developing world than industrialized regions. This may reflect variability in history and patterns of smoking, as well as background mortality from different diseases, and suggests that such factors should be explored in greater detail through direct observational studies, which are currently relatively limited for the populations in the developing countries of Africa and the Middle East.

Morbidity

Smoking is often the hidden cause of the disease recorded as responsible for a death because the use of tobacco acts as a major cause for many of the top killer diseases globally, including cardiovascular disease, chronic obstructive lung disease, and lung cancer [68].

Cardiovascular disease and risk factors for other disease

Cardiovascular diseases are the leading cause of death in high, middle- and low-income countries alike [68]. Tobacco smoking contributes significantly to cardiovascular morbidity and mortality. The effects of smoking extend to all phases of atherosclerosis from endothelial dysfunction to acute clinical events, the latter being mainly thrombotic. Both active and passive (ETS) smoke exposure predispose to cardiovascular events. Tobacco smoke increases inflammation, thrombosis, oxidation of low-density lipoprotein cholesterol, and oxidative stress, all of which contribute to cardiovascular dysfunction [69].

Results from the third National Health and Nutrition Examination Study (NHANES III) show that inflammatory markers (which provide indicators of atherosclerotic disease) return to baseline levels 5 years after smoking cessation. This suggests that the inflammatory component of cardiovascular disease resulting from smoking is reversible with reduced tobacco exposure and underlines the importance of smoking cessation [70].

Chronic obstructive pulmonary disease/respiratory diseases

Exposure to tobacco smoke is a significant risk factor for the development of COPD. Even after smoking cessation, this risk remains high for decades as the symptoms of COPD may become more apparent as lung function declines with aging [71]. The prevalence of COPD is predicted to rise dramatically in low- or middle-income countries, where more than 80% of the current smokers in the world live [71]. Buist *et al.* studied 9,425 people aged 40 and older from 12 countries to measure the prevalence of COPD and its risk factors. They found wide variations of COPD prevalence across the countries. Cape Town, South Africa, recorded the highest prevalence of combined stage II and III-plus COPD, with men at 22.2% and women at 16.7% [72]. The Lung Health Study showed that in patients with mild-to-moderate COPD, smoking cessation provides improvements in FEV_1 (airflow) and halved the decline in lung function relative to that in patients who continued to smoke [73].

Tobacco smokers are more likely to develop several other respiratory diseases, including emphysema, asthma, and tuberculosis (TB). The development of such diseases can be inter-related, for example tobacco smoking is associated with poorer outcomes in HIV-associated opportunistic infections, of which TB is the commonest in developing countries, while both smoking and TB are significant risk factors for the development of COPD [74]. In infants, exposure to EST, for example due to parental smoking in the home, increases the risk of bronchitis, bronchiolitis, and other lower respiratory infections [75]. In Africa and the Middle East, wider availability of smoking cessation and prevention programs is vital for limiting the economic and social impact of chronic respiratory diseases [76].

Cancers and tobacco

Carcinogens in tobacco which bind to DNA and cause genetic mutations are believed to provide the basis for the increased risk of lung cancer and other neoplastic diseases, including cancers of the oral cavity, oesophagus, stomach, pancreas, larynx, bladder, kidney, and leukemia in smokers [77, 78]. Almost 70% of cancer cases are in low- and middle-income countries, including those of the Middle East and Africa [79].

Lung cancer is of particular importance as, since 1985, this has been the most common cancer in the world, and an estimated 85% of cases in men and 47% of cases in women occur as a consequence of tobacco smoking [80]. In 2008, there were approximately 612,000 new cases and 539,000 deaths resulting from lung cancer in men in the developing world [81]. A study comparing the incidence of lung cancer across six Middle Eastern countries found that Qatar had the highest age-standardized incidence rate of 18.5 and 12.1 cases annually per 100,000 for males and females, respectively [82]. A further study examining the clinical and epidemiological characteristics of lung cancer cases in Qatar found that 82.5% of the patients were smokers or ex-smokers at the time of diagnosis [83].

In Africa, there is also considerable evidence linking tobacco with cancers. For example, in Sudan, oral cancer mortality is very high and has been linked to toombak use in men [84], in North African countries (Algeria, Morocco, and Tunisia) nasopharyngeal carcinoma was associated with both cigarette smoking and snuff use [85], and in South Africa, a rising prevalence of oesophageal cancer in black population males has been associated with pipe tobacco smoking [86].

The WHO predicts that by 2020 there will be 16 million new cancer cases per year and that 70% of these will be in the developing world [87]. Many of the smoking-related cancer cases are preventable and healthcare professionals throughout Africa and the Middle East must do all in their power to reduce this escalating burden of the tobacco epidemic.

Dependence, anxiety, depression, and withdrawal syndrome

Processed from fresh leaves of genus Nicotiana, which are harvested and cured to allow slow oxidation and degradation of carotenoids, the active substances in tobacco smoke trigger chemical reactions in nerve endings which heighten heart rate, memory, alertness and reaction time [88]. During smoking, dopamine and endorphins are released, which are associated with pleasure. Acetylcholine and nicotine possess chemical similarities, which allows nicotine to trigger cholinergic receptors (nicotinic acetylcholinesterase receptors) located in the central nervous system and nerve muscle junctions of skeletal muscles [89]. Because the effects of smoked tobacco last a few minutes, smokers experience withdrawal symptoms unless they continue to smoke [88]. Fakhfakh and co-workers have demonstrated such withdrawal symptoms in Tunisian smokers [90], while dependence, drug-seeking behavior, and abstinence-induced withdrawal symptoms have also been described in Syrian waterpipe smokers [91].

Metabolic syndrome

Tobacco smoke exposure is associated with metabolic syndrome in adolescents [92] and adults [93]. Components of the metabolic syndrome including insulin resistance, coronary artery disease (CAD), stroke, type 2 diabetes, and dyslipidemia are also associated with cigarette smoking [1, 94–96].

Brief exposure to ETS – acute vascular injury

Brief exposure to real-world levels of ETS (30 min of smoke yielding cotinine levels commonly observed in passive smokers) leads to sustained vascular injury characterized by mobilization of dysfunctional endothelial progenitor cells with blocked nitric oxide production [97].

Oral health

Numerous oral diseases are associated with cigarette and waterpipe smoking and the use of smokeless tobacco, including dental caries, gingivitis, oral ulcers, halitosis, oral cancers, oral leukoplakia, and oral candidiasis [98, 99].

Other health effects

Smokers have impaired wound healing, a reduced sense of taste and smell, lower resistance to infection, reduced physical endurance, premature skin aging, and higher rates of psoriasis, macular degeneration and cataracts resulting in blindness, peptic ulcer disease, osteoporosis, mental ill-health, and infertility than their non-smoking peers [1].

Smoking cessation: need for a chronic disease model

An understanding by clinicians and healthcare professionals of the chronic nature of tobacco dependence is important. Only a minority of tobacco users achieve permanent abstinence through their initial attempt to quit. The majority of users will persist in tobacco use for many years and typically cycle through multiple periods of remission and relapse. Tobacco dependence should therefore share the status of other chronic illnesses, with effective treatments given as long as is necessary to achieve successful clinical outcomes [100].

Surveillance

Tobacco surveillance involves the periodic collection of information about the patterns of tobacco use, tobacco prices, tobacco production, and tobacco control measures, etc. Tobacco surveillance systems that provide timely, reliable, and readily analyzable information on key indices of the tobacco problem to health workers in countries and regions worldwide are an important part of national and regional programs responding to the tobacco epidemic [15]. Such programs are required under Section 20 of the WHO FCTC [5].

South Africa provides a good example of effective implementation of tobacco surveillance activities within a developing country with limited resources [101]. The country actively monitors tobacco-related morbidity and mortality through the National Cancer Registry and death notification system (which includes a question on smoking history of the deceased). Information on tobacco usage, tobacco control policies, smoking initiation, and exposure to ETS is gathered through the All Media and Product Survey (AMPS) and performed annually. The comprehensive South African Demographic and Health Survey, which is performed at 5-year intervals, gathers data on adult smoking patterns, their opinions on the health effects of tobacco use and their exposure to ETS in the home and at the workplace, and tobacco-related morbidity. Smoking behavior and attitudes among the young are monitored regularly through the Youth Risk Behavior Survey (YRBS) and GYTS school-based questionnaire studies. Compliance of businesses with the smoke-free policy introduced in 1999 for bars, restaurants and other places of entertainment, and tar and nicotine content of cigarettes are also monitored. The National Council Against Smoking (NCAS), established in 1976, also plays a role in promoting education, legislation, treatment, and research to improve public health in South Africa by promoting non-smoking and cessation.

In the Middle East, countries are at varying levels in the development of surveillance and monitoring systems. In Bahrain, the need for greater liaison between government ministries regarding the tobacco market (import, export) and specific data on the amount of tobacco consumed, the type of tobacco permitted, the number of permitted smoking places, and other tobacco-related activities have been highlighted [102]. In response to the smoking epidemic in Syria, the SCTS has been established with a vision to "Promote scientific excellence and evidence-based public health in Syria and the Arab world" [43].

Specific genotypes conferring increased risk of tobacco dependency have been identified [103]. In Africa and Middle East countries, studies to ascertain the influence of genetic factors on the tobacco-dependence patterns in racial or ethnic subpopulations may help to tailor smoking treatment programs to improve their effectiveness [104].

Chapter 2 Role of policies in controlling tobacco use

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An introduction to tobacco control policies

The evidence against tobacco use is abundant, undeniable, and convincing; as is the need for urgent and immediate action to counter the global tide of tobacco-related morbidity and mortality [105]. As discussed in Chapter 1, the tobacco industry is dominated by transnational tobacco companies (TTCs). These companies execute marketing campaigns simultaneously throughout different countries and have co-ordinated cigarette smuggling in many countries. Harmonized international responses are thus needed to combat the tobacco epidemic effectively. The WHO has therefore developed the WHO Framework Convention on Tobacco Control (WHO FCTC) which reaffirms the right of all people to the highest standard of health and asserts the importance of demand reduction strategies, as well as supply issues to combat tobacco use [5]. Currently, 172 out of the 193 WHO member states are parties to the Convention, which entered into force on 27 February 2005 [106].

In addition to the WHO, many other healthcare bodies have developed and reviewed tobacco control policies [107, 108]. There is consensus that a comprehensive tobacco control policy should:

- offer a wide range of interventions
- be broad enough to allow for each country's diversity of cultural, social, political and economic factors
- target prevention of use in youth and young adults
- secure public support through education, awareness campaigns, pressure groups, and other strategies
- contain measures to reduce both demand for and supply of tobacco products
- install mechanisms to protect the environment [107, 108]

The WHO FCTC addresses all of the requirements above and defines international rules for tobacco control. Countries which become parties to the treaty commit to follow the Convention to guarantee the adoption of some, if not all, measures that, based on the opinions of the WHO, will effectively reduce tobacco consumption [107]. As might be expected when dealing with a set of global recommendations, some of the measures within the Convention are more acceptable and applicable to certain countries. For example, Zimbabwe and Malawi are neither signatories nor parties to the FCTC (see Chapter 1 for discussion on the role of tobacco production in the economies of these countries). Nonetheless, there are several important policy measures that tend to be adopted more readily by the majority of FCTC member states [107]. In low- to middle-income countries, such as those within Africa and the Middle East, the cost-effectiveness of any policy is likely to influence whether it will be implemented or not. The World Bank has identified six highly cost-effective policies to reduce demand for tobacco products which should be high on the list when developing public health policies:

1. Higher taxes on cigarettes and other tobacco products
2. Bans/restrictions on smoking in public and workplaces
3. Comprehensive bans on advertising and promotion of all tobacco products, logos and brand names
4. Better consumer information
5. Large, direct warning labels on cigarette boxes and other tobacco products
6. Support programs for smoking cessation [109]

A "core" combination of these policies, along with other relevant measures from the FCTC, can provide the basis for national or regional tobacco control programs which combine and co-ordinate educational, clinical, regulatory, economic, and social strategies [108]. The following sections will examine each of these six policies briefly.

1. Higher taxes on cigarettes and other tobacco products

Article 6 of the FCTC emphasizes the role of price and tax measures to reduce the demand for tobacco [5]. Price elasticity measures the responsiveness of a variable (e.g. cigarette sales) to a change in price. For every 10% increase in the price of cigarettes, it is estimated that a reduction of 2.5-5% in consumption occurs in high-income countries, while a reduction of up to 8% may occur in low- and middle-income countries [108, 110]. Increasing the price of tobacco products is one of the most effective ways to reduce tobacco use as it acts to prevent initiation (particularly among the young), reduces consumption among ongoing users, and encourages cessation [3].

The inverse relationship between cigarette consumption and real cigarette prices has been demonstrated in South Africa (see Figure 2 below).

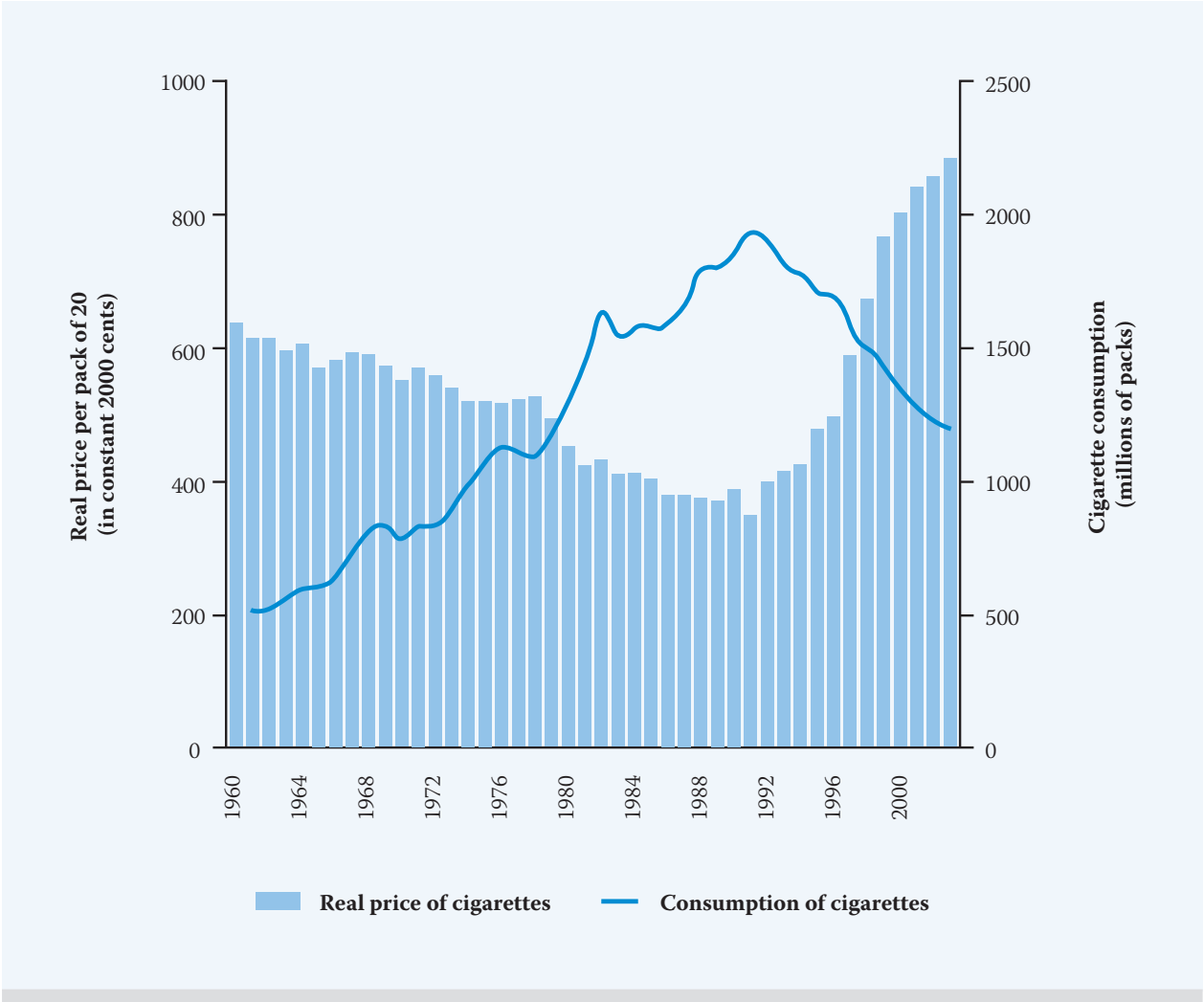

Figure 2: Inflation-adjusted cigarette prices and cigarette consumption, South Africa, 1961–2004 [111]

The World Bank recommends that cigarette taxes (including value-added or sales taxes) account for two-thirds to four-fifths of the retail price of a pack of cigarettes [109]. Few of the countries in Africa and the Middle East currently achieve this level of taxation, and most could significantly increase their tax levels [1, 110]. Increasing the price of cigarettes through higher taxes can also provide countries with funding to implement and enforce tobacco control policies, particularly if the revenue is earmarked for this purpose [1]. It has been suggested that in low-income and middle-income countries, taxation levels should target the "affordability" of cigarettes through pricing [112]. Research in China suggests that, as lower-income groups are particularly sensitive to pricing, reducing their cigarette expenditures through higher taxes can release household resources for spending on food, housing, and other goods that improve living standards [113].

Governments must recognize the long-term benefits from raising excise taxes, including reduced morbidity for those who will quit, cost savings (in terms of medical care costs), and increased working life and life expectancy. These benefits outweigh the argument that there may be a loss of revenue earned from taxes due to a decreasing number of smokers.

Recommendation: The authors of this guideline support the raising of taxes on cigarettes and other tobacco products as a proven means of discouraging smoking in the countries of Africa and the Middle East. The authors believe that reducing the affordability of manufactured cigarettes and tobacco in other forms, such as rolling tobacco, snuff, tobacco for waterpipes, etc., is essential to reduce the healthcare burden imposed by smoking and tobacco use.

2. Bans/restrictions on smoking in public and workplaces

Article 8 of the FCTC concerns protection from exposure to tobacco smoke [5]. Smoking bans provide benefits for both non-smokers and smokers. Non-smokers' exposure to environmental tobacco smoke (ETS) is reduced, while smokers tend to smoke less, have greater cessation success, and have increased confidence in their ability to quit [1]. As more countries are ratifying the FCTC, smoking bans in public places are becoming common and their effects on public health are already being reported [114, 115].

In the African region, South Africa, Niger, Nigeria and Kenya have played leading roles by introducing smoke-free laws and enforcing these. Mauritius has adopted a comprehensive smoke-free ban since 2009, which comes close to the standards set by the FCTC [116]. In Nigeria, the senate passed legislation in March 2011 to introduce one of the strongest anti-tobacco laws on the continent [117]. In the Middle East, progress has been slower, although recent theological rulings that tobacco is haram (prohibited under Islamic law) could support more acceptance of the harmful nature of ETS and favor more widespread adoption of smoke-free laws [116]. As waterpipe smoking is common in many countries in this region (see Chapter 1), it is vital that national smoke-free laws cover all forms of smoked tobacco. Countries should aim to avoid the experience in Iran, where pressure from the hospitality industry resulted in the Government granting an exemption to teahouses, allowing the smoking of unflavored tobacco to continue in these premises.

Recommendation: The authors of this guideline support the implementation of smoke-free environments in workplaces and public spaces in the countries of Africa and the Middle East. The specific legislation within each country should ensure that this protection is comprehensive and extends to cover all applicable commercial and non-commercial premises, for example airports, trains and bus stations, public transportation, restaurants, places of worship, sports venues, tourist attractions and leisure spaces and agricultural, fishing and mining facilities.

3. Comprehensive advertising and promotion bans for tobacco

Article 13 of the FCTC requires countries to implement a comprehensive ban on all tobacco advertising, promotion and sponsorship within 5 years of their ratifying the Convention [5].

Introducing a comprehensive advertising ban is associated with an estimated 6.3% reduction in per capita tobacco consumption [118]. Niger, Sudan, Botswana, South Africa, Eritrea, Madagascar, Djibouti, Jordan, Iran and Yemen have all banned direct and indirect marketing of tobacco [1]. In contrast, partial bans have little effect on smoking, as the tobacco industry can re-channel its marketing to other mediums [118]. Achieving public and political support for a comprehensive ban can be challenging, as the tobacco industry typically procures support and influence from other stakeholders like the media, sports industry, and cultural activity planners, who may be heavily dependent on tobacco advertising revenue. In Lebanon for example, despite ratification of the FCTC in 2005, tobacco control regulations remain weak as a result of an effective tobacco industry strategy to weaken the content and scope of such regulation, and to delay its adoption and implementation [19]. Nonetheless, advertising bans may be even more effective in the developing world than they are in the developed world [119]. Point-of-sale advertising bans have been implemented in around one-quarter and one-half of the countries of Africa and the Middle East, respectively, so there is opportunity for further improvement [1].

The tobacco industry uses both direct and indirect advertising strategies, therefore co-ordinated approaches should be used to tackle the full range of channels used, e.g. product placement within television and film, the use of communities following tobacco companies or products on online social networking sites, sponsorship of entertainment, sporting events, and organizations, etc. [47, 120]

Recommendation: The authors of this guideline support the introduction of comprehensive bans on the advertising and promotion of tobacco products. We encourage those countries of Africa and the Middle East which already have partial bans to extend these bans to cover all direct and indirect marketing activities, and for all countries in these regions to enforce advertising bans through appropriate sanctions and legal action. Enforcement of point-of-sale advertising bans should include retailers providing manufactured cigarettes and cigars, self-rolling tobacco products, pipe and waterpipe paraphernalia and smokeless tobacco products. Tobacco sales via vending machines should be regulated to ensure that no advertisements are visible on the equipment and that no purchases can be made by underage smokers. Bans must prevent indirect advertising to youth through sponsorship linking events such as music concerts and sports competitions with tobacco brands, and schemes offering loyalty rewards to tobacco users.

4. Better consumer information

Article 12 of the FCTC focuses on promoting and strengthening public awareness of tobacco control issues using all available communication tools [5]. Media campaigns can increase awareness and change attitudes about the risks of using tobacco and the benefits of quitting. "Information shocks" – for example, widespread dissemination of research findings showing the harmful effects of tobacco use on health – are particularly effective among populations in which knowledge of the health consequences of tobacco use is low, which can be the case in developing economies [110]. Dramatic real-life case studies can be used to highlight the impact of smoking side effects, e.g. a poster showing a cancerous lung removed from a smoker who has died from lung cancer or a leaflet showing effects of smoking on personal appearance (skin, hair, teeth) to counter the imagery of "glamour" which is often used in tobacco marketing. Other information shocks could include national statistics on smoking-related deaths, costs of smoking on family finances or the results from analysis of locally-purchased tobacco products highlighting the presence of toxins and the potential health implications for users of such products.

In countries where health education is under-funded and under-resourced, the tobacco industry has funded "youth smoking prevention programs" as a strategy to improve its public image [20]. Such industry-sponsored youth programs employ subversive measures to influence youth smoking uptake, for example by depicting smoking as an adult choice, while avoiding mentioning addiction and disease risks associated with smoking [1].

Recommendation: The authors of this guideline fully support the provision of medically accurate information on the negative effects of smoking and tobacco use throughout all countries of Africa and the Middle East. Education on these topics should be offered through multiple channels including those targeting youth (primary, secondary and tertiary schools/academies), members of the medical community (nursing and medical curriculum) and the general public (health centers, pharmacies, billboards, government websites, churches and mosques). Regular national and local campaigns should be delivered via posters, radio, television and print media to build and maintain awareness of the harmful effects of tobacco for the individual and society. Such materials should harness input and endorsement from relevant national experts and professional stakeholders, including health ministries and medical societies, and should be localized to reflect language and dialects within countries, as well as to address specific tobacco use patterns endemic to each region, for example use of waterpipes, smokeless tobacco, pipes, snuff, etc.

5. Large, direct warning labels on cigarette boxes and other tobacco products

Article 11 of the FCTC addresses the packaging and labeling of tobacco products [5]. Warning labels on cigarette packs are among the most widespread policy initiatives implemented to educate smokers [121]. Health warnings on cigarette packs are now mandatory in most countries around the world, and laws are steadily increasing the required size of the warning, strengthening the content, and enhancing the graphic design. In Canada, for example, the first health warnings appeared on cigarette packs in 1972, with a single voluntary statement placed by manufacturers in small print on the package. Since then, updates to Canadian federal legislation in 1989, 1994 and 2000 have increased the area which must be covered by warnings from 20% to 50% of the top area of the package front and back [122].

Depending on local rules, the warnings on the pack exterior may comprise text only or combine graphic images with text. Pull-out cards within packs can also be used to explain the health risks of smoking. Pictorial warnings are considered superior to text-only messages [123]. These are also associated with greater health knowledge, perception of risk, motivation to quit and cessation behavior. Pictorial messages are especially effective among youth, are essential for reaching smokers with low education and literacy, and can help in countries where multiple languages are common [124]. Pictures that arouse emotion through "graphic" depictions of health risks are most likely to be recalled and rated as effective by smokers and are not associated with adverse outcome [125]. There is a move in some countries (e.g. the UK, Canada, Australia and New Zealand) towards enforcing plain packaging with only brand name and health warning messages. This offers advantages in increasing the effectiveness of health warnings, reducing false health beliefs about cigarettes, and reducing brand appeal, especially among youth and young adults [126]. The tobacco industry is opposing such changes, arguing that plain packaging will facilitate counterfeiting and promote demand for black market imports of branded products.

The misconception that alternative non-cigarette tobacco products are less harmful should not be overlooked. As discussed in Chapter 1, the use of waterpipe tobacco smoking and smokeless tobacco products is increasing in Africa and the Middle East. Sales of these products are not currently regulated, so limited or no warnings exist. This was shown recently in a survey of waterpipe tobacco products and waterpipe accessories purchased from Lebanon, Dubai (UAE), Palestine, Syria, Jordan, Bahrain, Canada, Germany and South Africa, where no WHO FCTC-compliant waterpipe-specific health warning labels were found on any of the products examined from any of these countries [127].

Labeling tobacco products as mild, light or extra mild is misleading as the public can believe that the effects will be less harmful than "full flavor" or "regular" brands [128]. This branding terminology should be discouraged through laws targeting deceptive marketing strategies. There is no evidence to support a difference in health risks between low and high tar cigarettes.

Indeed, the nicotine, tar and carbon monoxide content printed on the package are inaccurate and misleading. Emission numbers are determined by a machine that "smokes" cigarettes according to a fixed puffing regime. This machine method does not predict the amount of smoke inhaled by individual consumers or account for design elements such as "filter ventilation" – tiny holes poked in the filter that lead to low emission levels under machine smoking, but much higher levels under human smoking. Smokers have also been shown to compensate for the reduced delivery of nicotine in order to achieve target nicotine doses, therefore increasing tar delivery [129]. As a result, there is no association between the machine-generated emission numbers printed on packages and the health risk of different brands [130].

Different countries apply varying rules about the size and position of warnings, but there is general agreement that the warnings should be clearly visible and cover a certain percentage of the front and back area of the packet. South Africa for example uses a system of rotating warning labels that appear in pairs on the front and back of the pack. The front health warning is brief and in large font, while the back warning provides more details on the front warning as well as a telephone number for those who want information or help quitting. In 2010, cigarette packs sold in Egypt featured a drooping cigarette image on the front of the box, with the message: "Smoking for a long period of time affects marital relations". In general, large printed text at the top portion of a packet provides greater visibility, while warnings appearing on the side of a pack are less impactful. Typically, warnings combine three elements: 1) graphic health warnings; 2) a toxic emissions statement; and 3) health information messages. More than 30 countries in Africa and the Middle East (Afghanistan, Angola, Azerbaijan, Bahrain, Botswana, Burkina Faso, Cape Verde, Central African Republic, Chad, Comoros, Congo, Equatorial Guinea, Ethiopia, Gambia, Guinea, Guinea-Bissau, Iraq, Kenya, Kuwait, Liberia, Malawi, Mali, Mauritania, Namibia, Nigeria, Oman, Rwanda, Sao Tome and Principe, Saudi Arabia, Senegal, Seychelles, Sierra Leone, Somalia, Swaziland, Tajikistan, Togo, Turkmenistan, Uganda, United Arab Emirates, United Republic of Tanzania, Zambia) currently do not have a legal requirement in place to include warnings on cigarette packs [1].

Recommendation: The authors of this guideline support the compulsory addition of warning labels on cigarette packets and other tobacco products in all nations of Africa and the Middle East as part of their healthcare policy efforts against the tobacco epidemic. We believe that the messages shown should combine both visual and text content, including text translated into all languages which are widely used within each country. Smokeless tobacco products, and waterpipe paraphernalia and tobacco should all carry warning labels similar to those used on cigarette packaging.

6. Support programs for smoking cessation

Article 14 of the FCTC calls upon all parties to the treaty "to develop and disseminate appropriate, comprehensive and integrated guidelines based on scientific evidence and best practices, taking into account national circumstances and priorities, and shall take effective measures to promote cessation of tobacco use and adequate treatment for tobacco dependence" [5]. The present guidelines document has therefore been conceived with public health workers, communities, non-governmental agencies and governments in mind. The contents include our efforts to describe the available non-pharmacological and pharmacological interventions (these are discussed in Chapters 3 and 4, respectively) which may be suitable for use in smoking cessation programs within Africa and the Middle East.

Recommendation: The authors of this guideline support the development and delivery of programs offering both non-pharmacological and pharmacological interventions for smoking cessation which are:

- easily accessible
- adequately staffed by well-trained professionals. Health workers, i.e. doctors, pharmacists, psychologists, nurses, social workers, etc., are best placed to lead the efforts

- targeted to educational institutions, health care facilities, workplaces and sporting environments as a priority

- a collaborative effort with both governmental and non-governmental agencies involved

Quantifying progress after policy implementation: Tobacco Control Scale

The 19th century British scientist Lord Kelvin noted, "If you can measure that of which you speak, and can express it by a number, you know something of your subject; but if you cannot measure it, your knowledge is meager and unsatisfactory". To quantify the implementation of tobacco control policies at country level, the Tobacco Control Scale has been developed and used to assess countries across Europe [131]. The scale is currently monitoring progress in 31 European countries and updated findings and rankings are published regularly [132]. The European countries' results for 2010 show that Slovenia improved its ranking by eight places (from 25th place among the 31 countries in 2007 to 17th place in 2010). This improvement was linked to the introduction of successful smokefree legislation in 2007. In contrast, Bulgaria dropped by 11 places (from 13th to 24th place). This was attributed to the significant lack of progress since 2007. Bulgaria has also not introduced comprehensive tobacco control legislation and continues to lack enforcement of existing smokefree legislation.

The Tobacco Control Scale assigns a maximum score for each of six measures considered to be essential components of a comprehensive tobacco control program (Figure 3). The scoring system was designed with the help of a panel of international tobacco control experts taking account of the relative effectiveness demonstrated for each of the six measures [131]. As an example, a country might score 20 out of a potential 30 points for "Price" control measures, 11 out of a potential 22 points for "Public bans" measures, and so on. If a country achieves full marks for all measures, the maximum potential score is 100. Countries are evaluated on the basis of how effective they have been in implementing policies regulating each measure. The six policy measures are those described by the World Bank [109] and considered earlier in this chapter.

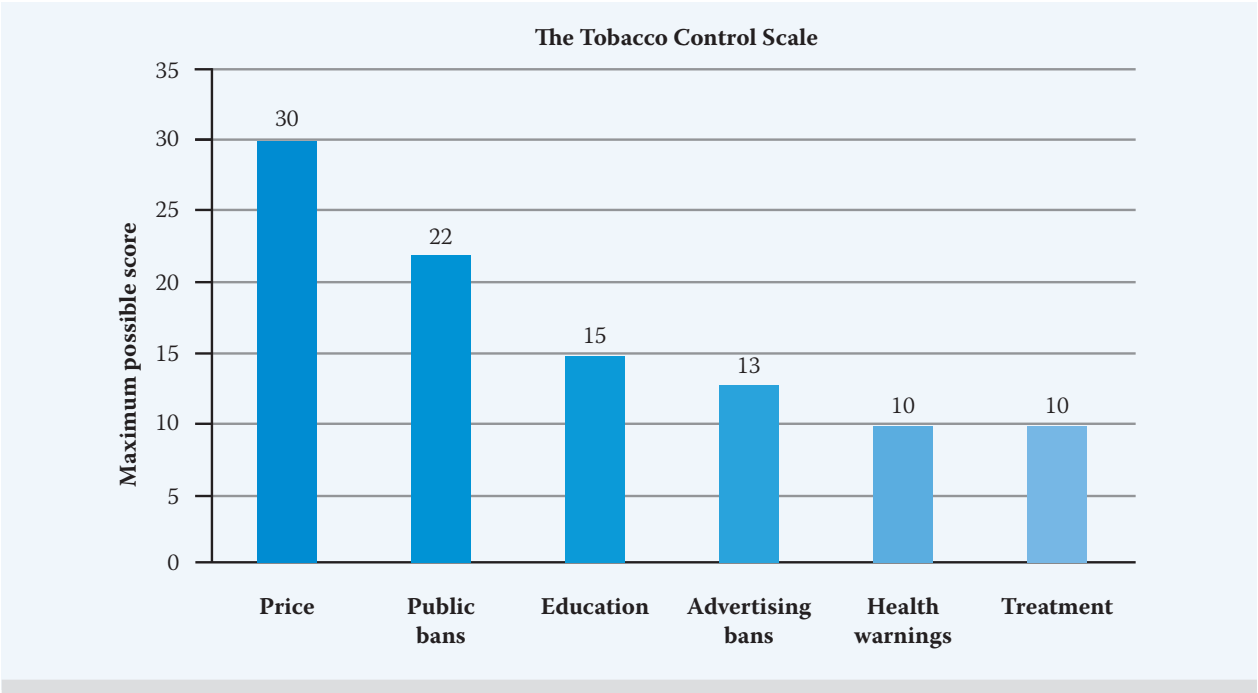

Figure 3: The Tobacco Control Scale (maximum potential scores for each measure shown above each bar) [131]

The Tobacco Control Scale may provide a useful model for monitoring progress after tobacco control policy implementation in Africa and the Middle East. The scale also allows disparities between countries to be highlighted and may motivate countries to improve their performance if they are shown to be falling behind others in the region.

Chapter 3 Non-pharmacological interventions

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Introduction

Article 14 of the WHO FCTC recognizes that programs for diagnosing, counseling, preventing, and treating tobacco dependence should include both non-pharmacological- and pharmacological-based interventions [5]. Smoking cessation treatments consist of psychological (behavioral) support and pharmacological support to counter tobacco dependence. Many national and international clinical guidelines addressing tobacco dependence have been developed and perhaps the most comprehensive and influential to date is the US Public Health Service Guideline for Treating Tobacco Use and Dependence 2008 Update [133]. This guidance, along with recommendations from other countries, including the UK National Institute for Health and Clinical Excellence (NICE) 2006 guidelines [134] and the Latin American Tobacco Dependence Treatment Healthcare Professionals Coalition 2010 [2], has provided valuable perspectives to the authors of the present document as we sought to develop guidelines which take into account the circumstances and priorities of African and Middle Eastern countries. Our guidelines incorporate the US Public Health Service's "5As" – Ask, Advise, Assess, Assist, Arrange – model for a brief intervention in the primary care setting [133]. However, for individual cases and to reflect local cultural issues, it is recommended that one also considers the ABC (Ask about smoking status; give Brief advice to stop smoking to all smokers; provide evidence-based Cessation support for those who wish to stop smoking) algorithm from the New Zealand Ministry of Health 2007 guidelines, which may be easier to implement as this has fewer steps to consider (see Figure 9 in the Appendix) [135].

Non-pharmacological interventions feature prominently in all of the guidelines mentioned above and this chapter provides our recommendations for implementing these strategies effectively. The use of pharmacological interventions is described in Chapter 4. It is important to stress that the combination of counseling and medication may be more effective than either alone [136], so clinicians should use an individualized approach when choosing the most effective treatment strategy or strategies to use for each patient.

What are the health benefits of quitting?

The health benefits of tobacco cessation begin within minutes of a smoker quitting and these benefits continue to increase steadily over time (Figure 4) [137].

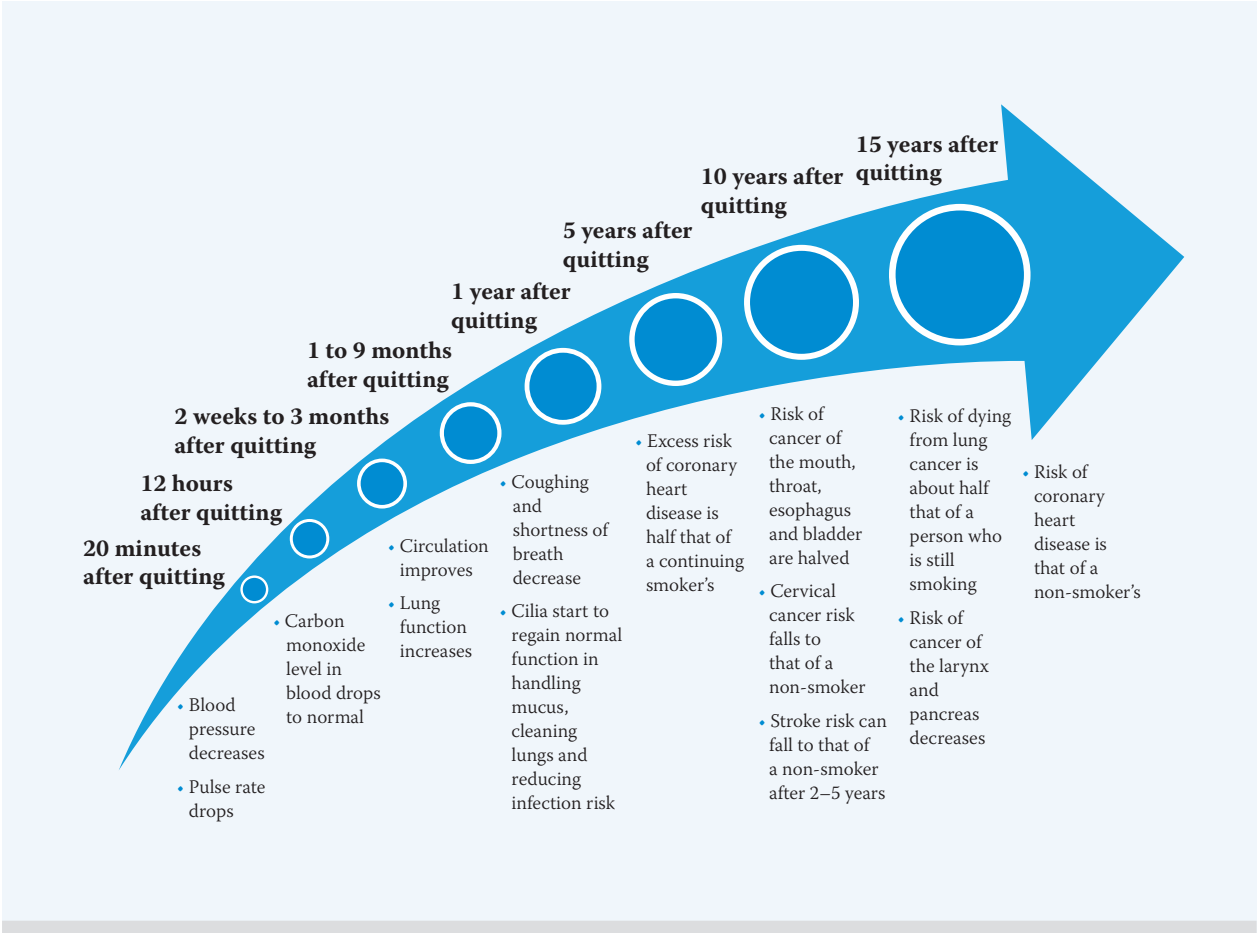

Figure 4: Health benefits of tobacco cessation over time [137]

The stages of change model

The "stages of change" model behavioral approach has been applied to smoking [138] and has proven useful in adapting or tailoring treatment to the individual [139]. This model is used for example within the intervention steps within the US Public Health Service guideline [133] and those within the NICE guidelines in the UK [134]. This approach assumes that smokers pass through a discrete series of motivational stages:

Pre-contemplation: the individual does not perceive their smoking to be a problem and has no intention of quitting in the foreseeable future (typically over the next 6 months).

Contemplation: the individual is aware that their smoking is a problem, and is thinking seriously about overcoming it but has not committed to a course of action. Contemplators may state that they are seriously considering changing their behavior within the next 6 months.

Preparation: individuals intend to take action within the next month, and have unsuccessfully taken action in the past year.

Action: the person makes overt behavioral changes to stop smoking, and has successfully altered their behavior for a period of anything from 1 day to 6 months.

Maintenance: the now ex-smoker works to prevent relapse and to consolidate their abstinence for more than 6 months.

Relapse: the ex-smoker resumes smoking. This may be a partial relapse in response to a single triggering event or a complete relapse in which the ex-smoker resumes smoking as part of a regular routine.

The model proposes that individuals move sequentially through the stages, but may revert to earlier stages before finally achieving complete abstinence. Support from a therapist can help the individual to prepare for each step and to progress from one step to the next. For example, after a relapse, the therapist encourages the patient to re-enter the contemplation or preparation stage in order to make a further attempt to quit [138, 139].

a) Incorporating smoking cessation into primary care

Primary care providers (PCPs, including general practitioners, community nurses, traditional birth attendants, and community health workers) have the opportunity, credibility, and authority to provide smoking cessation advice and are effective in assisting smokers to quit [140]. Integrating tobacco cessation into primary healthcare and other routine medical visits provides opportunities to remind users that tobacco harms their health and others around them. By repeating this advice at every medical visit, the benefits of stopping tobacco use are reinforced [141].

Beyond basic training for healthcare workers on cessation counseling and development of informational materials for tobacco users, significant investment is not required. This treatment approach can also mobilize healthcare workers and patients to support other tobacco control efforts.

In the interval that patients spend waiting to see their primary healthcare provider, health promotion information can be conveyed via a notice board and patient education materials. Brief information-gathering questionnaires can also be used in the waiting room to collect information on behavioral risk factors such as smoking.

Smoking cessation support can be delivered via both brief and intensive interventions. Brief interventions (less than 10 minutes) provide advice and encouragement to all smokers to quit and point them towards effective treatments that can help. These interventions can reach a wide population as only minimal time and resources are required for delivery. Intensive interventions (discussed in more detail later in this chapter) require more time and resources, so these may have a narrower reach, but higher success rates [142].

Within a primary care setting, the goal of brief intervention strategies is to ensure that every patient who uses tobacco is identified, advised to quit, and offered scientifically sound treatments. It is essential to provide at least a brief intervention to every tobacco user at each healthcare visit and responsibility for this should lie with both the clinician and the healthcare system [133].

Identification and assessment of tobacco use

The first step in treating tobacco use and dependence is to identify tobacco users [133]. The identification of smokers itself increases rates of clinician intervention. Effective identification of tobacco use status opens the door for successful interventions through clinician advice and treatment, and guides clinicians to identify appropriate interventions based on patients' tobacco use status and willingness to quit. Clinicians and healthcare systems should therefore use every office visit for universal identification and assessment of tobacco use (Figure 5).

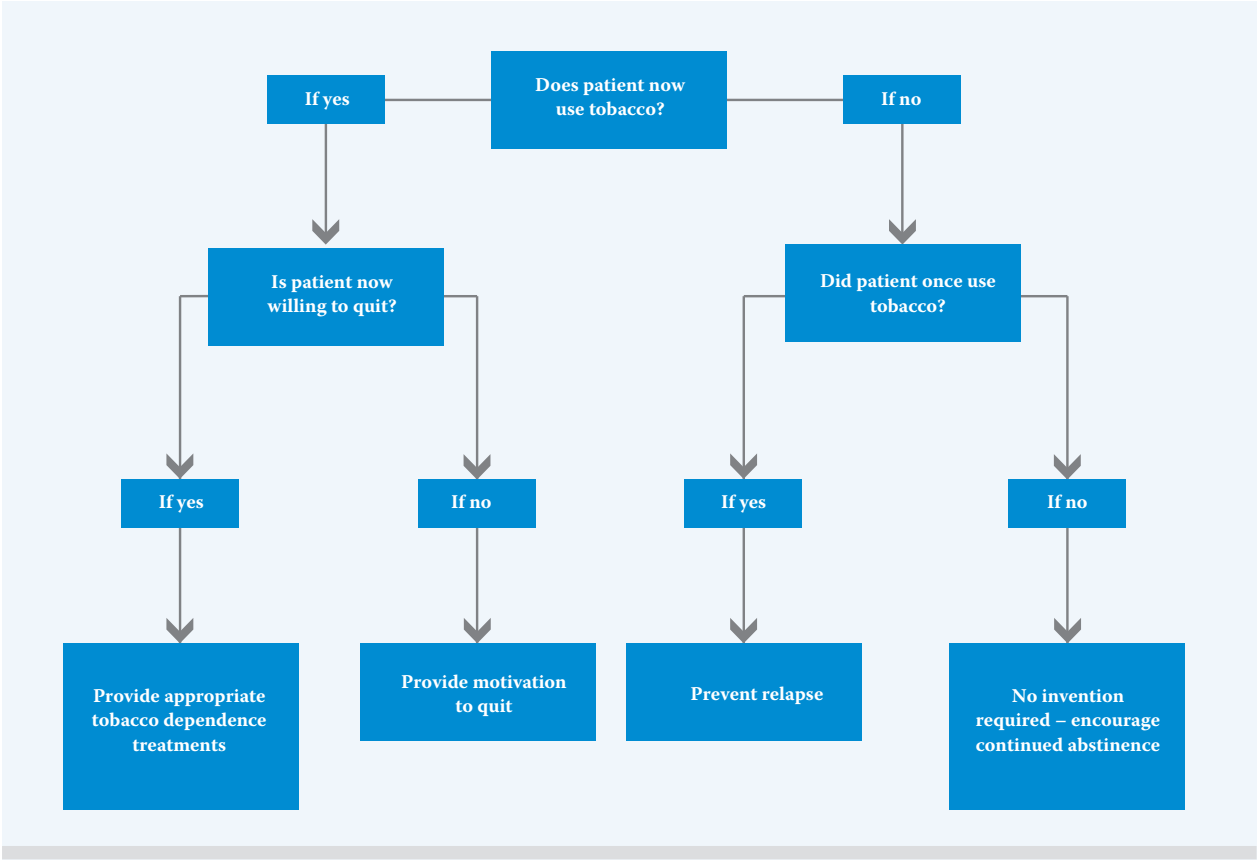

Figure 5: Algorithm for treating tobacco use [133]

As illustrated above, this approach will result in four possible responses: 1) a patient uses tobacco and is willing to make a quit attempt; 2) a patient uses tobacco, but is not willing to make a quit attempt; 3) a patient previously used tobacco, but has already quit; and 4) a patient never regularly used tobacco. Based on these responses, the clinician can then provide the appropriate intervention, either by assisting the patient in quitting (the 5As) or by providing a motivational intervention (the 5Rs, discussed later in this chapter). The following sections provide interventions for the first three patient groups (the fourth group does not typically require further intervention, other than to provide encouragement to continue to refrain from tobacco use).

i) For the patient willing to quit

The 5As model for brief intervention tobacco cessation counseling in the primary care setting is shown schematically below (Figure 6) and the components are summarized in Table 8.

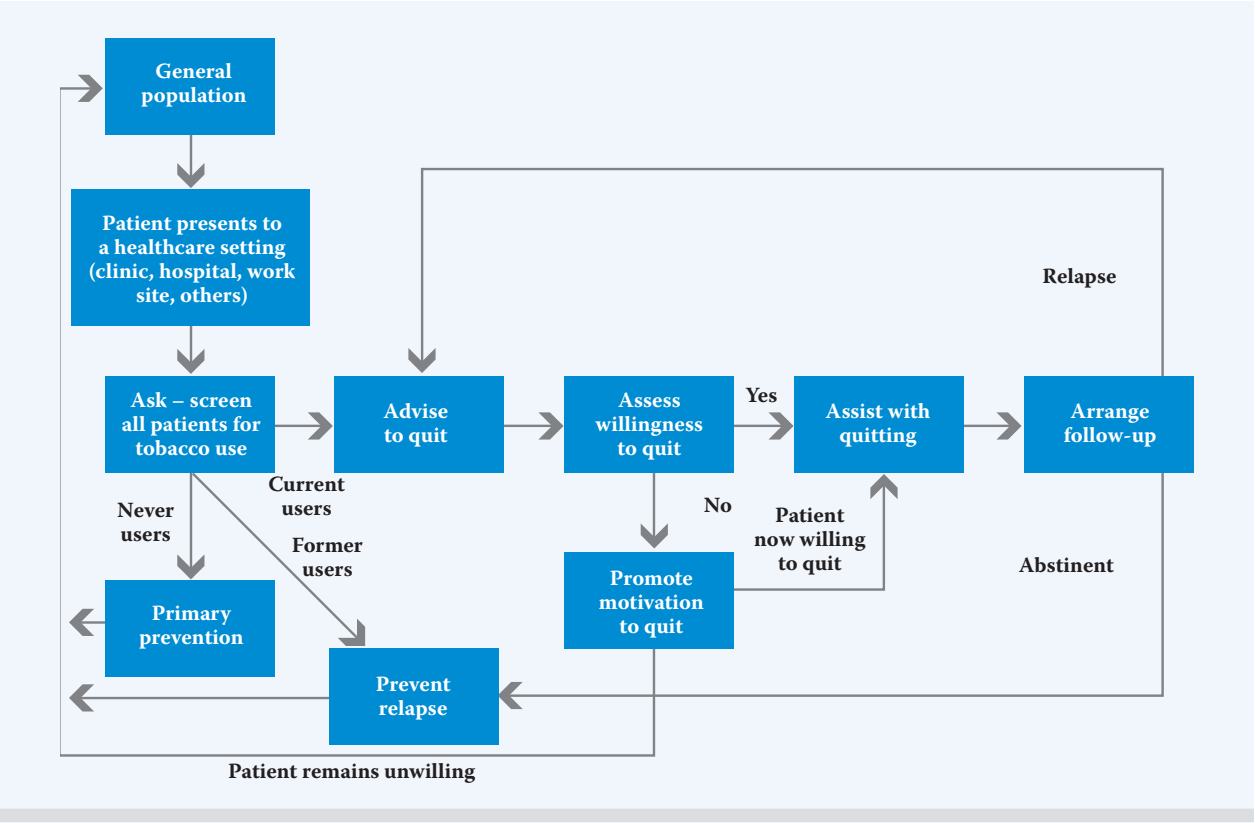

Figure 6: The 5As model for treatment of tobacco use and dependence in primary care [133]

Ask about tobacco use.	Identify and document tobacco use status for every patient at every visit.
Advise to quit.	In a clear, strong, and personalized manner, urge every tobacco user to quit.
Assess willingness to make a quit attempt.	Is the tobacco user willing to make a quit attempt at this time?
Assist in quit attempt.	For the patient willing to make a quit attempt, offer medication and provide or refer for counseling or additional treatment to help the patient quit. For patients unwilling to quit at the time, provide interventions designed to increase future quit attempts.
Arrange follow-up.	For the patient willing to make a quit attempt, arrange for follow-up contacts, beginning within the first week after the quit date. For patients unwilling to make a quit attempt at the time, address tobacco dependence and willingness to quit at next clinic visit.

Table 8: Steps in the 5As model for treating tobacco use and dependence [133]

The strategies in the 5As model are designed to be brief and require 3 minutes or less of direct clinician time. Implementation can be achieved by a clinician (e.g. a physician, dentist, physician's assistant, or nurse practitioner) with support from others (e.g. a medical assistant or a health educator) who can deliver additional treatment to the patient. The clinician would remain responsible for the patient receiving appropriate care and subsequent follow-up, but, as with other sorts of healthcare, an individual clinician would not need to deliver all care personally.

Ask

In the course of identifying a smoker, asking is the first step. Unfortunately, health professionals, including doctors and nurses, do not always identify smokers. For example, a survey in Australia found that GP doctors identified only 56% of their patients who smoke [143], while more recently a study in Scotland identified that self-reporting of smoking behavior by pregnant women may underestimate the incidence of smoking in this group [144].

A questionnaire on smoking history can be filled in by the patients while waiting for their appointment. This assessment can gather information on the patient's level of addiction to tobacco, readiness to quit, history of serious quit attempts, and any support used for these, as well as any barriers to cessation.

If smoking status is unknown, all patients should be asked and smoking status documented from age 16. It may also be appropriate to ask patients aged 10–16 about smoking if this is relevant to the presenting complaint (e.g. respiratory presentations, such as asthma, upper respiratory tract infection (URTI), etc.) and during discussions about drug misuse issues.

Ask: "Do you smoke?" and "Have you ever smoked?" Once a current smoker is identified, the doctor or practice nurse can take a brief smoking history as follows:

- Number of cigarettes smoked per day or per week and the year of starting smoking
- Previous quit attempts and what happened
- Presence of smoking-related disease

Smoking status should be documented as current smoker, ex-smoker, or never smoked. The amount (number of cigarettes or equivalent per day) and year of commencement of smoking should also be documented. For ex-smokers, the quit date should be recorded. To ensure smoking status is easily identified within medical records, this could be included as an extra field in vital signs information, or denoted by attaching a color-coded sticker to patients' notes [133].

Assessment of tobacco dependence will help to predict whether a smoker is likely to experience nicotine withdrawal on stopping smoking, thus helping a therapist to select the most appropriate level of non-pharmacological and/or pharmacological support that will be needed. Dependence and withdrawal can develop with all forms of tobacco. Features of tobacco dependence include: smoking soon after waking, smoking when ill, difficulty refraining from smoking, reporting the first cigarette of the day to be the most difficult to give up, and smoking more in the morning than in the afternoon. The modified Fagerström Test for Nicotine Dependence (FTND) [145], recently renamed the Fagerström Test for Cigarette Dependence (FTCD) [146], is a widely used and validated 6-item questionnaire to assess severity of nicotine dependence, with scores ranging 0–10 (Figure 7). Recently, it has been proposed that two of the FTCD questions are more critical and informative than the others [147]. It has been suggested that most of the predictive power is accomplished by asking just two questions: 1) How soon after you wake up do you smoke your first cigarette?; and 2) How many cigarettes per day do you smoke? These two questions have thus been used as a short version of the full FTCD and this approach may be useful for busy physicians, whereas for scientific trials, one can still use the full 6-item test to allow comparisons with data from other studies.

The Lebanon Waterpipe Dependence Scale (LWDS-11) is an instrument for measuring waterpipe smoking dependence for both research and clinical purposes [148]. The LWDS-11 arose from a rigorous development and validation process and is the only instrument described to date that measures dependence among waterpipe users [149]. The LWDS-11 questionnaire is composed of 11 scale items in 4 subscales measuring tobacco dependence (4 items), negative reinforcement (2 items), psychological craving (3 items), and positive reinforcement (2 items). Each item is scored on a 4-point scale and a total score of 10 is used to indicate dependence.

Questions for determining cigarette dependence *(FTCD)*

How soon after you wake up do you smoke your first cigarette?	
Within 5 minutes	3
6–30 minutes	2
31–60 minutes	1
>60 minutes	0
Do you find it difficult to refrain from smoking in places where it is forbidden?	
Yes	1
No	0
Which cigarette would you hate to give up most?	
The first one in the morning	1
Others	0
How many cigarettes per day do you smoke?	
≤10	0
11–20	1
21–30	2
≥31	3
Do you smoke more frequently during the first hours after waking than during the rest of the day?	
Yes	1
No	0
Do you smoke if you are so ill that you are in bed most of the day?	
Yes	1
No	0
Addiction score:	**Level of addiction:**
0–2	Very low
3–4	Low
5	Medium
6–7	High
8–10	Very high

Figure 7: Fagerström Test for Cigarette Dependence (FTCD) [145, 146]

Advise

The importance of physician-delivered advice in encouraging patients to quit is well recognized [133]. However, again there is evidence that not all doctors may provide such support. For example, in an Australian survey only 34% of doctors reported offering cessation advice during every routine consultation with a smoker [150] and an Italian survey found that only 22% of smokers received advice to quit smoking from their physician in the previous year [151].

Irrespective of whether they want to stop smoking or not, advise all smokers to quit smoking using brief, repetitive, consistent, positive reminders. Examples of advice are given in Table 9.

The advice used should depend upon the clinician, the smoker, and also the situation in which it is given. Brief advice appears to be most effective in less dependent smokers [152]. For more dependent smokers, it is important that brief advice is followed by a recommendation to use smoking cessation medication and referral to a smoking cessation service. All doctors should provide brief advice to quit smoking at least once a year to all patients who smoke [133].

Type of message	Examples
Clear	"I think it is important for you to quit smoking now, and I can help you/I can refer you to a specialist." "Cutting down while you are ill is not enough." "Occasional or light smoking is still dangerous."
Strong	"As your doctor, I need you to know that quitting smoking is the most important thing you can do to protect your health now and in the future. I will help you and you will not suffer from the withdrawal symptoms."
Personalized	Tie smoking to the patient's current health/illness, and/or social and economic costs of tobacco, and/or impact on children or other household. Use the history, physical exam finding and significant life events to further personalize advice. "Your heart condition became worse." "You are currently having a progressive chest disease COPD." "Your child's asthma will not improve unless you quit." (In males, it is important to emphasize that smoking could lead to impotence.)
Supportive and non-confrontational	Inform the patient about the advantages of quitting and that there are treatments to help. Any smoker identified should be advised to stop smoking. "I have several patients who have successfully quit using this program." "Your work is very stressful, but there are ways to help you cope with this which will help reduce your tobacco dependence."

Table 9: Examples of advice messages for treating tobacco use and dependence [133]

Assess

The third step in the process involves assessing whether the tobacco user is willing to make a quit attempt. The standard approach for many smokers has been to quit abruptly on a designated quit day. For example, in a household survey among smokers and ex-smokers in the UK, almost half reported having made a quit attempt without any preplanning [153]. However, recent studies show comparable quit rates after reducing the number of cigarettes smoked before quit day compared with quitting abruptly, with no prior reduction in smoking beforehand [154]. In addition, a recent meta-analysis of randomized, controlled trials that tested smoking-reduction interventions (pharmacological, behavioral, or both combined) among smokers who were not ready to make a quit attempt (immediately or in the next month) found that smoking-reduction interventions significantly increased long-term abstinence from smoking [155].

If the patient is willing to make a quit attempt now, provide assistance (see the fourth step Assist, which follows). If the patient is unwilling to make a quit attempt at the time, provide motivational intervention to increase future quit attempts (see the later section on the second type of patient: For the patient unwilling to quit) or to encourage smoking reduction as a precursor to a future quit attempt. Regardless of which stage the patient is at, being patient-centered and non-judgmental is useful in all approaches [138, 139]. Examples of questions for assessment are given in Table 10 [133].

Assessment objective	Examples
Express concern/interest, and not criticism	"How do you feel about your smoking at the moment?", "Are you ready to quit now?"
Discuss reasons and motivations for wanting to quit	"What are your motivations for wanting to quit?", "Are you concerned about the effects of second-hand smoke on others?"
Understand past unsuccessful attempts	"What types of triggers or situations trigger your tobacco use?", "Did you involve your social network of friends, family, and coworkers?", "Was pharmacotherapy used as instructed?"
Support confidence	"Many smokers like you have succeeded in beating their addiction", "Do you have concerns about weight gain or withdrawal symptoms?"

Table 10: Examples of questions to assess a patient's willingness to quit tobacco use [133]

Assist

If the patient is willing to make a quit attempt, the clinician can assist either by referring the patient to a Tobacco Treatment Specialist (TTS), or treating the patient directly. Immediate actions should include helping the patient to develop a quit plan which sets a quit date, identifies opportunities for removing triggers and temptation for smoking, and harnesses support from family, social contacts, and a smoking cessation support counselor/TTS. If pharmacological-based interventions are appropriate for the patient, recommend the use of medication which is approved and available, and explain how the medication can increase quitting success and reduce withdrawal symptoms [133].

The clinician should provide counseling on practical cognitive and behavioral strategies at this stage. Cognitive strategies focus on retraining the way a patient thinks. For example, many quitters panic because they are thinking about tobacco after they quit, and this leads to relapse. Patients can be taught that thinking about cigarettes (or other forms of tobacco) is normal and the impulse to resume use can be overcome. Behavioral strategies involve specific actions for coping with the effects of quitting and reducing risk for relapse. This can include the patient ensuring that their environment is tobacco-free areas (e.g. in the home and workplace) and using oral substitutes (e.g. drinking water or chewing sugar-free gum) to replace tobacco. These counseling approaches help the patient to recognize danger situations, to develop coping strategies, and to gain a greater understanding of the challenges they will face as a result of quitting and the duration of these hurdles.

Doctors and healthcare givers should ensure that the patient has a supportive clinical environment which encourages the individual's attempt to quit. Information on supplementary resources available outside the clinic should be made available, e.g. details of national quit-lines (if available), support groups, and information booklets adapted for local culture/language, etc.

Other ways to facilitate the quitting process at this stage include:

- Ensuring the patient understands the difference between a slip and a full relapse. A slip is a situation in which a person smokes one or just a few cigarettes. Although this can lead to a full relapse, it is not a complete failure, and it should be considered part of the learning process. If a slip occurs, the patient should be encouraged to think through the scenario and determine the trigger(s) for smoking. Suggest coping strategies that will enable the patient to avoid smoking in similar situations

- Discussing withdrawal symptoms and explaining that most of these symptoms disappear within 4 weeks of abstinence. (See section on nicotine replacement therapy (NRT) withdrawal symptoms in Chapter 4 for further details on withdrawal symptoms commonly encountered)

- Explaining that some weight gain may occur after quitting smoking (3–5 kg for women and men, respectively)[156, 157], but that diet, exercise, and medication can limit this effect. Emphasize that the health benefits from stopping smoking are greater than any risk arising from the weight gain that may occur

- Initiating self-monitoring by the smoker. Keeping a "diary" or record of the number of cigarettes smoked at the beginning of the treatment, and timings and feelings when cravings are experienced, which is kept updated during the quit attempt, can increase awareness of smoking behavior and help to identify situations with a high risk for relapse [133]

Arrange

The last of the 5As is to "arrange follow-up". At this point, the clinician should summarize treatment plans and offer to assist throughout the quit attempt. Follow-up contact is recommended within the first week after quitting and at 2–3 weeks later, with additional follow-up contact as needed until the patient is stable as an ex-user of tobacco. Withdrawal symptoms will be at their worst during the first days after quitting and will decline over the following weeks [158].

At follow-up contact, it is important to reassess the patient's commitment to quitting and confidence in quitting. The clinician should query any problems encountered, so that additional resources and referrals (e.g. to other healthcare providers, telephone cessation lines, etc.) can be offered as required. Follow-up cessation counseling can be done face-to-face if the patient is scheduled to return for a clinic appointment. Alternatively, follow-up may be done over the telephone.

If the patient has remained abstinent at the time of follow-up, they should be congratulated on this success and the importance of remaining abstinent emphasized. If the patient has resumed smoking at the time of follow-up, the clinician should discuss the circumstances which led to the slip or full relapse. The patient should be urged to recommit to total abstinence and alternative counseling support strategies or pharmacological support offered as appropriate.

ii) For the patient unwilling to quit

Patients may be unwilling to make a quit attempt for several reasons (e.g. a lack of understanding of the harmful effects of tobacco use and the benefits of quitting, concern about the costs involved for smoking cessation, and low morale after earlier attempts at quitting failed) [133]. Motivational interviewing (MI) is a counseling technique for helping people to explore and resolve their uncertainties about changing their behavior. This approach has been widely used to help people stop smoking and has proven effective when given by GPs and by trained counselors [159].

The content areas that should be addressed in an MI counseling intervention for smoking cessation can be captured by the 5Rs: relevance, risks, rewards, roadblocks, and repetition [160]. Clinicians should discuss the relevance of quitting smoking in terms of its effects on the smoker's lifestyle and health. This discussion should also outline the risks of smoking (including focusing on effects which may be most relevant for the individual (e.g. cardiovascular disease, skin damage, impotence, cancer risk, etc.)), and the rewards of quitting (e.g. financial, health benefits for oneself and family members). Potential roadblocks associated with quitting, such as potential weight gain and nicotine withdrawal symptoms, should be acknowledged. This will assist the patient in developing practical strategies to overcome such roadblocks. Finally, the clinician must explain that quitting is a process of relapse and repetition for most people; repeated attempts to quit smoking are a common and accepted pathway to abstinence [133, 160].

Scheduled reduced smoking is a technique where the smoker follows a schedule to gradually reduce smoking by increasing the time between cigarettes smoked, until only a few are smoked per day [161]. Pharmacological support, such as NRT, may be beneficial during the smoking reduction phase (see Chapter 3 for details on NRT use). This approach can assist future cessation; however, it is only recommended for patients unable or

unwilling to quit using alternative methods. Scheduled reduced smoking weakens the link between urges to smoke and lighting up, increases confidence in the ability to quit, and provides opportunities to practice coping strategies between scheduled cigarettes. It can also move smokers along the behavioral model towards the ultimate goal of quitting [161, 162].

iii) For the patient who has recently quit

Patients who continue to abstain

Relapse is common among smokers as they attempt to quit [163]. The critical time frame for relapse is during the first 3 months of abstinence, with the first few days following the quit date being most crucial [164]. To help prevent relapse, the clinician should counsel the patient about the benefits, milestones, and difficulties of quitting smoking and encourage continued abstinence [133].

Relapse prevention interventions should include a discussion of the benefits the patient has experienced through quitting, challenges encountered during the process, successes in resisting relapse, and potential barriers to continued abstinence (e.g. stress or social events involving smokers). Clinicians should empathize with the patients who experience a sense of loss after quitting and reassure them that such feelings will subside over time.

For patients who are using pharmacotherapy regimens but continue to experience strong withdrawal symptoms, consider adding, combining, or extending the use of medications.

Assist in resolving any residual problems: if there is weight gain, make recommendations for use of a diet plan and exercise; if the patient reports persistent negative moods, refer them to specialist support; if the patient feels there is a lack of support or that their motivation is flagging, offer telephone or group support [133].

Patients who have recently relapsed

Clinicians should reassure the patient that even unsuccessful attempts to quit should be valued as these show that the patient is willing and able to take the first steps. Discuss with the patient what factors precipitated the relapse, and help identify strategies to overcome these in the future. Encourage them to fix another quit date and discuss the option to try other methods of cessation support if appropriate [133].

b) Intensive interventions

Intensive interventions (i.e. more comprehensive treatments that may occur over multiple visits for longer periods of time and that may be provided by more than one clinician) are appropriate for any tobacco user willing to participate in this form of treatment. As intensive tobacco dependence treatment is more individualized, this is more effective than brief treatment [165, 166].

A multi-disciplinary approach is used, involving relevant TTSs who have had training in smoking cessation counseling (e.g. GPs, dental care professionals, and psychiatric care experts). The process should begin with an assessment to determine whether a tobacco user is willing to use an intensive treatment program to make a quit attempt. Assessments of other factors at this stage (e.g. stress level, dependence) can provide useful information for counseling [133].

When possible, the intensity of the program should be more than 30 minutes for the first session and as long as required for subsequent sessions, with a minimum of four sessions and preferably more. Both individual and group-counseling formats which include practical behavioral and cognitive strategies are effective. Combining counseling and medication increases abstinence rates [133]. Therefore, as part of intensive interventions, smokers should be offered medications which have established effectiveness (see Chapter 4 for details on pharmacological-based interventions for smoking cessation).

c) Telephone support

Tobacco quit-lines with trained staff should be accessible to a country's entire population through toll-free telephone numbers. Quit-lines are inexpensive to operate, easily accessible, anonymous for users, and can be staffed to ensure that tobacco users can call outside regular daytime business hours. These services can also allow individuals in remote places to access support.

Quit-lines linked to counseling services are even more effective in helping people overcome tobacco addiction [133]. Telephone support can be reactive (where the smoker calls a helpline for information and advice) or proactive (where the smoker receives calls from a telephone counselor at set times). The strongest evidence for efficacy exists for the proactive form of telephone support [167]. Some quit-lines have also expanded onto the internet, providing continuous availability of free support materials and links to other services [168].

d) Face-to-face support

Face-to-face support, either on an individual basis or in a group situation, has been shown to help people stop smoking. Quit rates are generally higher when medication is used in combination with face-to-face support. Both individual and group-based interventions are effective. A mobile smoking cessation service can help in reaching patients who have difficulty traveling to access health services (e.g. the elderly or those in remote areas) [169].

The clinician provides the same guidance and medication that would be used in individual treatment; however, group interventions provide the patient with additional opportunities to share their experiences and to benefit from peer support. Running effective group treatment requires input from trained TTSs. Ground rules should be established to allow the group to function effectively (e.g. to ensure that discussions remain private and that all members of the group are treated equally). Meetings can end with a commitment from all participants to refrain from smoking until their next regular meeting [133].

e) Other methods used in smoking cessation intervention

Acupuncture

Acupuncture is a traditional Chinese therapy, typically using needles to stimulate particular points in the body. In smoking cessation, acupuncture is used with the aim of reducing the withdrawal symptoms. Despite the availability and use of these treatments in many countries, a recent Cochrane analysis has concluded that there is no consistent, bias-free evidence that acupuncture or the related treatments acupressure, laser therapy, or electrostimulation are effective for smoking cessation [170].

Hypnosis

Several types of hypnotherapy are used in smoking cessation. Some methods try to weaken the smoker's desire to smoke, strengthen their will to quit, or help them concentrate on a "quit program". Currently, there is limited evidence to support hypnotherapy as an effective alternative to counseling treatment [171].

Deep relaxation training

The stress response is both psychological and physical, and for many people this triggers the desire to smoke. Learning and practicing deep relaxation techniques can reduce feelings of stress. Deep relaxation results in decreased heart and respiration rates, blood pressure, and muscle tension. With continued practice, deep relaxation can improve sense of wellbeing and ability to cope with life stressors. Ways to accomplish relaxation include deep abdominal breathing, progressive or passive relaxation, meditation, guided imagery, and self-hypnosis [172].

f) Special populations

1. Pregnant smokers

Female smokers have lower fertility levels and therefore have lower rates of successful conception [1, 173]. In females, nicotine affects the production of hormones that are necessary for pregnancy and this is thought to reduce fertility [174]. Smoking also inhibits normal transportation of the egg through the Fallopian tubes to the womb, which may explain the increased incidence of tubal infertility and ectopic pregnancy observed in women who smoke [175].

Smoking during pregnancy is harmful for both the mother and growing fetus. Tobacco smoke toxins damage placental function and reduce the amount of oxygen available to the developing fetus

[176, 177]. Maternal smoking during pregnancy is the largest modifiable risk factor for intrauterine growth retardation [178]. During pregnancy and up to the time of birth, other adverse effects of smoking include increased risks of placental abruption, abortion, or placenta previa [173, 178].

Mothers who smoke are more likely to give birth prematurely and their babies have a lower birth weight [178]. These infants require more frequent medical attention and hospitalization [179], have a higher risk for sudden infant death syndrome [180], and are more likely to develop attention deficit hyperactivity disorder [181] relative to children whose mothers did not smoke during pregnancy. Young children are also particularly vulnerable to the effects of environmental tobacco smoke (ETS).

Intervention

- Pregnant smokers should be strongly encouraged to quit throughout pregnancy, from as early in the pregnancy as possible and into the post-partum period

- Because of the serious risks of smoking to the mother and the fetus, pregnant smokers should be offered intensive counseling treatment. When pregnant women stop smoking there are benefits for both the mother and child

- Cessation efforts should be encouraged in all women of child-bearing age who smoke. If intensive measures are not feasible, the strongest possible interventions should be used and include motivational messages regarding the impact of smoking on both the pregnant smoker and fetus

Note: the use of pharmacological treatments, including NRT to help pregnant women stop smoking, is discussed in Chapter 4.

2. Breast-feeding women

Smoking leads to a significant reduction in breast milk volume [182] and increases the likelihood of early weaning [183]. Nicotine from tobacco or ETS freely passes in and out of breast milk, depending on the concentration of nicotine in the maternal blood [184]. The relatively low level of nicotine exposure due to breast-feeding (approximately 7 mg/kg/d [184]) is not believed to be harmful to the infant and is outweighed by the benefits of breast milk over bottle-feeding [185]. Encouraging breast-feeding among women who quit smoking because of pregnancy may help motivate post-partum smoking abstinence, while increasing adherence to current infant feeding guidelines [186].

Intervention

- As mentioned previously, smokers should be strongly encouraged to quit throughout pregnancy and into the post-partum period. If addicted mothers cannot stop smoking, it is vital to encourage and support breast-feeding

Note: the use of pharmacological smoking cessation treatments, including NRT and bupropion, in breast-feeding women is discussed in Chapter 4.

3. Psychiatric comorbidities

People with mental health and addictive disorders smoke at high rates and require tobacco treatment as a part of their comprehensive psychiatric care [187, 188]. Exceptionally high smoking rates have been observed among patients with anxiety disorders, depression, and schizophrenia, and in individuals with a history of alcohol or drug abuse or dependence [189]. However, several barriers can limit their access to smoking cessation support. Psychiatric care providers may fail to address tobacco use among people with mental illness, which may be due to low expectations that their patients will be able to quit successfully, or fears that even short-term abstinence will adversely influence psychiatric status [187]. In addition, individuals with mental illness may use smoking as a coping mechanism or a form of self-medication [190], so may also be less likely to present themselves for tobacco dependence treatment.

More widespread integration of smoking cessation support within chemical dependence or mental health clinics is recommended [191]. It is also important to recognize that patients with mental health problems

are at higher risk of relapse following smoking cessation [192] and so require ongoing support.

A harm-reduction model for patient care should include tobacco dependence treatment within mental health and addiction treatment settings as: 1) tobacco use is a leading cause of mortality in patients with psychiatric illness or addictive disorders; 2) tobacco use is associated with worsened substance abuse treatment outcomes, while treatment of tobacco dependence supports long-term sobriety; 3) tobacco use is associated with increased (not decreased) depressive symptoms and suicidal risk behavior; 4) tobacco use negatively impacts psychiatric treatment; 5) tobacco use is a lethal and ineffective long-term coping strategy for managing stress; and 6) treatment of tobacco use does not harm mental health recovery [193].

Intervention

- In patients with psychiatric comorbidities (e.g. depression, eating disorders, anxiety disorder, attention deficit disorder, or alcohol abuse), strongly consider referral to intensive counseling
- Close monitoring of the patients' mental health during smoking cessation is recommended
- In patients taking medication to treat mental health disorders (e.g. the antipsychotics clozapine or olanzapine), tobacco smoke may speed up the metabolism of such drugs, so dosage adjustment and/or drug level monitoring may be needed when such patients stop smoking

4. Children and adolescents

In children and adolescents, tobacco use has the potential for nicotine addiction, for other smoking-related damage, and increases the risk for alcohol and drug abuse [194]. Although Article 16 of the WHO FCTC prohibits the sales of tobacco products to persons under the age set by domestic law, national law, or 18 years [5], smoking rates among the young remain a challenge in many countries. For example, in South Africa, Lesotho, Mauritania and Burkina Faso, 16.0–29.9% of male students aged 13–15 smoke cigarettes [1]. In Africa and the Middle East, parents may wrongly perceive that smoking tobacco via waterpipe is much safer than cigarette-smoking in school children and be more permissive towards this [65, 194].

Those who do not smoke before the age of 20 are significantly less likely to start smoking as adults, therefore programs for young people should address both prevention and treatment [195]. Clinicians should ensure that they deliver tobacco prevention and cessation messages to pediatric patients and their parents [196]. Most young smokers make attempts to quit which are not supported by available behavioral and pharmacological treatments, despite evidence showing that young people who enroll in a tobacco cessation program are twice as likely to succeed in their quit attempt [195, 197].

Intervention

- Clinicians should question pediatric and adolescent patients about tobacco use and provide them with clear information regarding the importance of totally abstaining from it
- Adolescents who smoke should be offered counseling interventions to aid them in quitting smoking
- To protect children from second-hand smoke and inappropriate role model behavior, clinicians should ask parents about tobacco use and offer them cessation advice and assistance
- Cessation interventions shown to be effective with adults should be considered for use in children and adolescents. The content of these interventions should be modified to be appropriate for the developmental stage of the patient

Note: the use of pharmacological smoking cessation treatments, including NRT and bupropion, in adolescents is discussed in Chapter 4.

5. Hospitalized and pre-operative patients

Patients with tobacco-related illness may gain significant benefits from stopping smoking, even after many years of heavy smoking. Quitting greatly reduces health risks and produces immediate and long-term health benefits [1]. Patients who smoke and undergo surgery are at increased risk of wound infection, delayed wound healing, and post-operative pulmonary and cardiac complications [198–200].

Inpatients may be more open to help at a time of perceived vulnerability, and may find it easier to quit in the hospital environment where smoking is restricted or prohibited. Initiating smoking cessation services during hospitalization may help more people to make and sustain a quit attempt [201].

Intervention

- All hospitals should have systems set up for helping patients to stop smoking. This includes providing advice to stop smoking and either providing a dedicated smoking cessation service within the hospital or arranging for referral to an external smoking cessation treatment program

- High intensity behavioral interventions that begin during a hospital stay and include at least 1 month of supportive contact after discharge are effective in promoting smoking cessation among hospitalized patients

- Primary prevention of smoking should also be pursued as a goal within healthcare systems. This is particularly important for those African countries which are in Stage 1 of the WHO/ Lopez smoking epidemic model, where tobacco use is driven by factors such as smuggling, availability of locally grown tobacco products, and social smoking or tobacco use (e.g. waterpipe, smokeless tobacco, and snuff). Non-governmental organizations should be involved to maximize the impact of such primary prevention initiatives through meetings in mosques, churches, and other public places

Chapter 4 Pharmacological interventions

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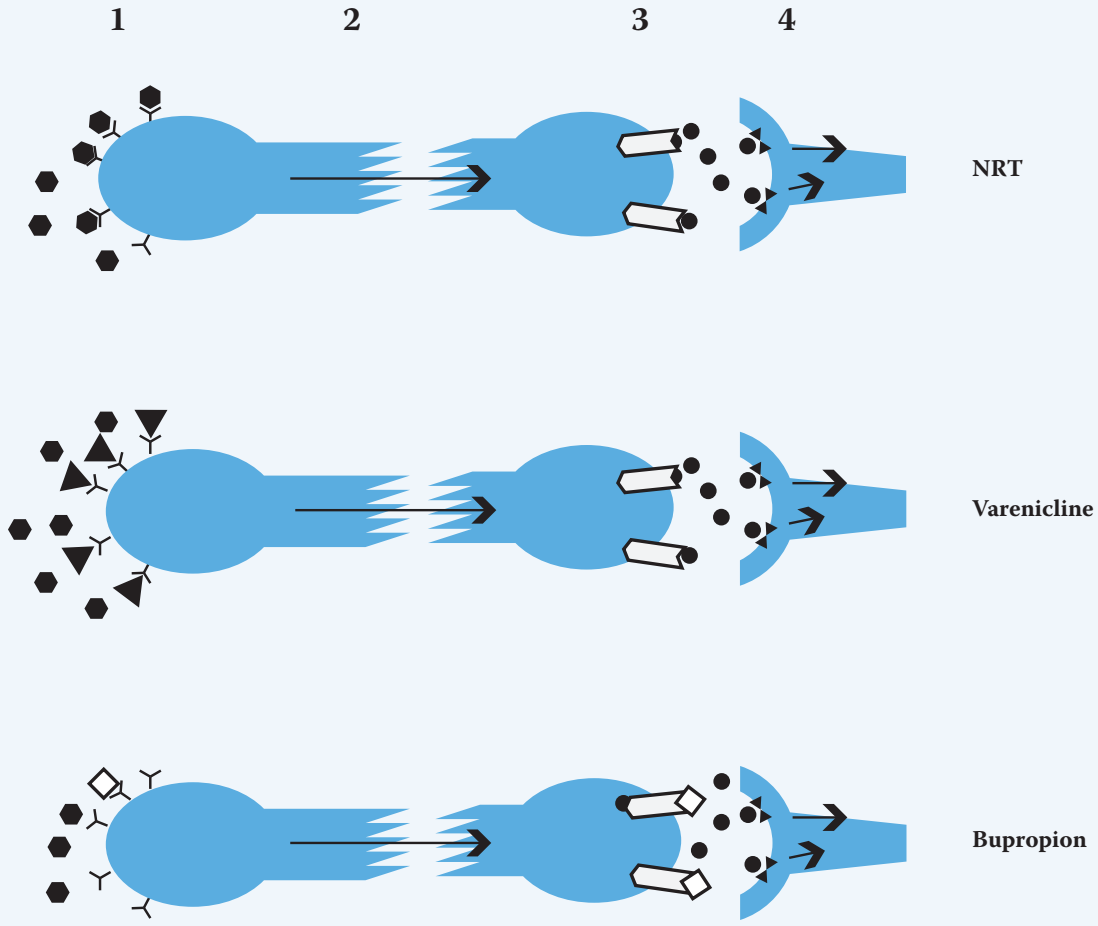
Introduction

This chapter presents an overview of pharmaceutical aids for smoking cessation available in Africa and the Middle East. There are three officially recognized first-line medications: nicotine replacement therapy (NRT) (with several formulations), bupropion hydrochloride and varenicline [133]. Several second-line medications will also be discussed. Three tables at the end of the chapter indicate: a) suggested details for clinical use of pharmacotherapies in smoking cessation (Table 11); b) effectiveness and abstinence rates for various medications and medication combinations compared to placebo (Table 12); and c) currently available medications for smoking cessation in the Africa and Middle East region per country (for countries with available data) (Table 13). We advise doctors to refer to the full prescribing information for each product in their country for appropriate use of these medications.

Neurobiological actions of first-line therapies

A brief consideration of the neurobiological background to actions of the first-line pharmacological options for smoking cessation may be useful at this point. Nicotine in tobacco stimulates (by acting as an agonist) nicotinic acetylcholine receptors (nAChRs) found in the nervous system. The a4-β2 nAChR is believed to be the receptor that lies at the heart of nicotine dependence and is concentrated in the ventral tegmental area (VTA) of the brain, which is closely linked via a dense supply of dopamine neurons to the brain's reward center (the nucleus accumbens) [202]. Stimulation of a4-β2 nAChR by nicotine releases excessive amounts of dopamine, which is associated with feelings of pleasure. Repeated stimulation by nicotine leads to sensitization and the development of addiction and smoking rituals over time. When nicotine is not supplied (for example when a smoker attempts to quit), cravings and withdrawal symptoms occur, as the subtle reinforcing effects of nicotine are removed. NRT, varenicline and bupropion each have different effects on nicotinic receptors and dopamine release (Figure 8) [202, 203].



Nicotine replacement therapy (NRT) partly replaces the nicotine from smoking. Nicotine (black hexagons) activates nicotinic acetylcholinic receptors (nAChRs) [1] present on the cell body of dopamine neurons in the ventral tegmental area, triggering rapid firing of the dopamine neuron [2] and the release of dopamine (black circles) via dopamine transporters [3] located on the neuron terminal in the shell of the nucleus accumbens. The released dopamine binds to dopamine receptors on the post-synaptic membrane [4] resulting in sensations of pleasure/reward.

Varenicline (black triangles) blocks nAChRs, but its partial agonist effects still trigger dopamine release (black circles), so reducing cravings which would occur if the nucleus accumbens was not stimulated following withdrawal of smoking-stimulated dopamine release. Varenicline also blocks the rewarding effect if a cigarette is smoked.

Bupropion (black diamonds) inhibits re-uptake of dopamine by occupying the dopamine transporter, thereby increasing the amount of dopamine to bind to post-synaptic dopamine receptors. Thus, initiating treatment with bupropion while reducing smoking helps to reduce cravings and maintains the rewarding effect of nicotine until total cessation. Bupropion also acts as a non-competitive inhibitor of the nAChRs.

Figure 8: Simplified overview of the effects of NRT, varenicline and bupropion on nicotinic receptors and dopamine release [202, 203].

Nicotine replacement therapy

As discussed in Chapter 1, the powerful pharmacologic agent nicotine is the main psychoactive compound in tobacco that leads to addiction [88]. A smoker absorbs 1–3 mg nicotine per cigarette regardless of nicotine-yield ratings on the box [204]. Nicotine intake triggers the release of catecholamines (which include dopamine), vasopressin, endorphins, cortisol, and adrenocorticotropic hormone (ACTH). These biochemical changes lead to addiction as smokers experience pleasure, increased arousal, decreased anxiety and decreased hunger with increased metabolic rate [10, 88]. Within hours of cessation of smoking, smokers begin to experience the nicotine withdrawal syndrome that peaks at 48 hours. Symptoms of nicotine withdrawal include: craving, anxiety, restlessness, irritability, depressed mood, increased appetite, and difficulty concentrating [10, 89].

The rationale behind NRT is that the administration of nicotine in a controlled and supervised fashion will help to avoid or at least decrease withdrawal symptoms [10, 205]. Thus, although NRT does not completely relieve withdrawal symptoms, it makes the experience of stopping more bearable. NRT supplies nicotine without the toxic and carcinogenic components of tobacco smoke and is highly cost-effective [206]. First introduced as chewing gum, NRT is now available in several formulations, all of which are safe for almost all types of patient [205].

In NRT, nicotine is delivered in different ways depending on the formulation, i.e. via the oral mucosa for chewing gum, lozenges, sublingual tablets and inhaler/inhalator formulations; or via the skin for transdermal patches. All of these commercially available forms of NRT are effective as part of a strategy to promote smoking cessation and the choice of which form to use should reflect patient needs, tolerability, and cost considerations. NRT is also safe to use in repeat attempts to quit by people who have relapsed after a previous attempt [205].

Nicotine replacement medications should not be viewed as stand-alone treatments that help smokers to quit. Reassurance and guidance from health professionals can be critical to achieve and sustain abstinence [207].

Special considerations

Close compliance with the prescribed regimen is important if pharmacotherapies are prescribed for smoking cessation. Patients should be advised to take the medications as prescribed, not as needed. Nicotine replacement therapies have a slower onset of action relative to inhaled tobacco smoke. If a patient waits until he or she is in dire need of nicotine before taking NRT, it may be too late.

Use of NRT in patients with cardiovascular disease (CVD)

Importantly, NRT can be safely used in people with stable CVD [208, 209]. NRT releases lower levels of nicotine at a steady pace into the venous system compared to active smoking, and provides none of the many other compounds contained in cigarette smoke. CVD patients using NRT are therefore in a less hazardous situation than those who continue to smoke [205, 210].

CVD patients in the acute phase, such as dependent smokers currently hospitalized as a result of myocardial infarction, severe dysrhythmia or cerebrovascular accident and who are considered to be hemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions [211]. If this fails, NRT may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision.

Use of NRT in pregnant and breast-feeding women

NRT can be used by women who are pregnant once they have been advised of and have assessed the potential risks and benefits. Manufacturers' NRT product information states that nicotine passes to the fetus affecting breathing movements and has a dose-dependent effect on placental/fetal circulation [211]. However, the risk to the fetus when using NRT is lower than that expected with tobacco smoking, as the slower delivery of nicotine results in lower maximal plasma concentration. In addition, NRT avoids the fetal exposure to polycyclic hydrocarbons

and carbon monoxide which occurs due to smoking or environmental tobacco smoke exposure during pregnancy [212]. Expert opinion suggests that the use of NRT in pregnancy carries only a small potential risk to the fetus, but it is far safer than smoking [213, 214].

Because the benefits of breast-feeding outweigh the risks of nicotine exposure, nicotine is not contraindicated during breast-feeding [215]. Nicotine from smoking and NRT passes into breast milk [211]. However, the amount of nicotine the infant is exposed to is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed to. NRT should be considered when a breast-feeding mother is unable to quit, and when the likelihood of quitting, with its potential benefits, outweighs the risks of NRT and potential continued smoking [212].

Use of NRT in adolescents

Although NRT has been shown to be safe in adolescents (12–18 years), there is insufficient evidence to suggest that the use of NRT by adolescents who smoke improves continuous 6-month abstinence rates [195]. As a result, NRT is currently not recommended as a component of tobacco use interventions for adolescents [133]. Nevertheless, expert opinion is that NRT may be considered for use by dependent adolescents who want to stop smoking [216]. The dose and method of use are as for adults; the recommended treatment duration is 12 weeks [211].

Side effects with NRT

Symptoms of nicotine overdose include nausea, salivation, abdominal pain, diarrhea, sweating, headache, dizziness, disturbed hearing and marked weakness. In extreme cases, these symptoms may be followed by hypotension, rapid or weak or irregular pulse, breathing difficulties, prostration, circulatory collapse, and terminal convulsions [211].

Withdrawal symptoms from NRT

Symptoms related to nicotine withdrawal are similar to those encountered after withdrawal from smoking. These symptoms include irritability/aggression, dysphoria/depressed mood, anxiety, restlessness, poor concentration, increased appetite/weight gain, urges to smoke (cravings), night-time awakenings/sleep disturbance, and decreased heart rate [10, 211].

Contraindications to NRT

NRT should not be administered to patients with known hypersensitivity to nicotine or any component of the NRT product. The NRT formulation used should reflect patient needs, for example patients with temporomandibular joint disease should not use NRT gum and NRT nasal spray should not be used by patients with an active gastric or duodenal ulcer, or by those with chronic nasal conditions.

Recommendations for NRT dosage

Table 11 at the end of this chapter provides different NRT doses for different daily smoking levels. Start with a higher dose for 2–4 weeks, and then decrease to a lower dose for 2 weeks and so on. The different formulations of NRT provide alternate methods for delivery and have slightly different onsets of action and duration. It is important to follow the manufacturers' guidance for approved NRT products marketed within each country as the dosage strengths and frequency of administration vary from product to product.

As far as the different dosages and recommended durations for the different formulations within the NRT range are concerned, it is the consensus of the co-authors of this guideline that in clinical practice all of these products are best used ad lib. For the duration of such treatment, the maxim is: treat as long as required to achieve cessation of tobacco dependence. There is evidence that higher NRT doses [205, 217], and longer NRT treatment duration [205, 218] can improve cessation outcomes, especially in high dependency smokers.

NRT formulations

Transdermal nicotine patches

Nicotine patches deliver nicotine through the skin at a steady rate. Several patch formulations are on the market; these vary in their design, pharmacokinetics, and duration of wear (e.g. 16 or 24 hours) [219]. For some products (e.g. Nicorette® or Nicotinell® patches),

progressively lower doses can be used to provide weaning over a period of several weeks or longer to enable gradual adjustment to lower nicotine levels and ultimately to a nicotine-free state.

Smokers who use more than 10 cigarettes per day should use the 21 mg/day patch for the first 6 weeks, move to the 14 mg/day strength for 2 weeks, and then use the 7 mg dose for the final 2 weeks. Nicotine patches have higher compliance than other NRT products but may not adequately protect against craving provoked by smoking-related stimuli. For breakthrough cravings not adequately controlled by transdermal nicotine alone, acute therapies may be added, for example referral for counseling on practical cognitive and behavioral strategies (see Chapter 3) or combining transdermal NRT with another form of NRT such as gum.

- The patch should be applied at the same time each day, usually at the beginning of the day. The patch should be applied to a non-hair, clean and dry area above the waist, front or back or upper part of the arm; it should not be applied on burned, broken, cut or irritated skin. Alternating the application site will help to prevent such problems

- Important side effects of the nicotine patch include skin irritation, itching, abnormal dreams or difficulty sleeping, diarrhea, and indigestion. These effects often reduce over time. It is normal for the patch to cause some tingling or mild burning when first applied. These sensations should go away in an hour. The skin under the patch may be red for a day after removal. If this persists or the skin becomes swollen, discontinuation or dose adjustment is recommended. Undesirable side effects are headache, gastrointestinal discomfort, nausea, vomiting, erythema, and reversible atrial fibrillation

Nicotine gum

First introduced in the 1980s, nicotine polacrilex (nicotine gum) is available without prescription in many countries [219]. The gum is available in two doses: 2 mg and 4 mg, delivering approximately 1 mg and 2 mg of nicotine respectively. Users are instructed to use a piece of gum every 1–2 hours for the first 6 weeks, then to reduce use to one piece every 2–4 hours for 3 weeks, and one piece every 4–8 hours for 3 weeks. In highly-dependent smokers, the 4 mg gum is superior to the 2 mg gum. Since only about 50% of the nicotine in gum is absorbed, a fixed schedule of 10 pieces per day will provide a smoker with about 10 mg or 20 mg of nicotine per day using the 2 mg or 4 mg gum, respectively. The maximum dosage should not exceed 24 pieces per day.

The slow absorption of nicotine from the gum does not produce the extremely high levels of nicotine measured through active smoking. Acidic beverages interfere with buccal absorption of nicotine. Patients should avoid acidic beverages (e.g. soda, coffee) for 15 minutes before and during chewing gum. Nicotine gum chewing may cause jaw soreness; therefore, the smoker should chew the gum to release nicotine, and then move the gum between the cheek and gum. The gum can also cause a mild burning sensation in the mouth and throat, which may be undesirable.

The gum is placed in the mouth, moistened, and bitten down once or twice to release the peppery taste, then "parked" between the cheek and gum. It should be chewed slowly and intermittently, and parked for about 30 minutes on fixed schedule (one piece every 1–2 hours) for 8 weeks. This medicine should not be chewed like regular chewing gum.

Lozenge

Lozenges are available in 1, 2, and 4 mg formulations [219]. Nicotine from the lozenge is absorbed slowly via the buccal mucosa. Generally, patients should use one lozenge every 1–2 hours during the first 6 weeks of treatment, using a minimum of nine lozenges a day, then decrease lozenge use to one lozenge every 2–4 hours during Weeks 7–9, and then decrease to one lozenge every 4–8 hours during Weeks 10–12. The lozenge should not be chewed, and the amount of nicotine absorbed per lozenge is higher than that delivered by gum.

Inhaler

An NRT inhaler is a small plastic tube containing a replaceable nicotine cartridge. It consists of a mouthpiece and a plastic cartridge containing nicotine. When the inhaler is "puffed" nicotine is drawn into the mouth of the smoker and satisfies the behavioral aspects of smoking, i.e. the hand-to-mouth ritual [219].

- Each inhaler cartridge contains 10 mg of nicotine, of which 4 mg can be delivered and 2 mg are absorbed. Nicotine is not delivered to the bronchi or lungs, but rather it is deposited and absorbed in the mouth, like nicotine gum. Most people use between 6 and 16 cartridges a day; the recommended duration of treatment is 3 months, after which patients may be weaned by gradual reduction over the following 6–12 weeks

- The user should puff on the inhaler every 20 minutes. After four 20-minute puffing sessions, the cartridge should be changed

- In cold weather, it is advisable to keep the inhaler warm to help the nicotine vapor be released from the cartridge

Nasal spray

The nasal spray is available as a prescription medication. It delivers nicotine more rapidly than other NRTs and relieves acute craving. The multi-dose bottle with a pump delivers 0.5 mg of nicotine per 50 μL squirt. Each dose consists of two squirts, one to each nostril. The dose of nasal spray should be individualized for each patient based on the patient's level of tobacco dependence. Most patients start with one or two doses per hour, which may be increased up to the maximum of forty doses per day [219].

Sublingual tablet

A small nicotine tablet has been launched in certain countries (for example available in South Africa as Nicorette® Discreet Variant, or as Nicorette® Microtabs in other areas where marketed). The product is designed to be held under the tongue, where the nicotine in the tablet is absorbed sublingually. The levels of nicotine obtained by use of the 2 mg tablet and 2 mg nicotine gum are similar [220]. It is recommended that smokers use the product for at least 12 weeks, after that the number of tablets used is gradually tapered. The tablet is designed to dissolve completely [219]. The number of tablets used per day is dependent on how many cigarettes were smoked. If a patient had smoked up to 20 cigarettes per day, the recommended dose is one tablet every hour. If this level is not sufficient to relieving cravings, the dose can be increased to two tablets every hour. If a patient smoked more than 20 cigarettes per day, they should use two tablets every hour. For all patients, the maximum daily dose is 40 tablets [221].

Mouth spray

A mouth spray of 1 mg per actuation of nicotine has been available in South Africa for many years (marketed as Quit™). Nicotine is dissolved in a highly concentrated alcohol solution. The recommendations are ad lib use, but formal studies evaluating this spray are lacking. However, a similar newer product (Zonnic® Mouth Spray, NicoNovum) has been tested in South Africa as well, and has been found to be comparable in efficacy and safety to other NRT formulations [222]. A further product, Nicorette QuickMist® Mouth Spray [223] has recently been launched in Europe and may be approved for marketing in countries of Africa and the Middle East in the future. Both Zonnic® and QuickMist® contain ethanol as an excipient, however less than 100 mg of ethanol is delivered per spray dose so there is minimal risk of intoxication, although non-users of alcohol may prefer to use alternative NRT formulations.

Recent advances in NRT use

NRT for smoking reduction

There is evidence that combined reduced smoking and concurrent NRT use is successful [224] and leads to a reduction of surrogate markers for smoking-induced health effects [225], and increases subsequent smoking

cessation [226]. Smoking reduction should never be seen as an alternative for smoking cessation, but rather as a first step in the right direction for recalcitrant smokers unable or unwilling to quit.

Pre-treatment with NRT before target quit date

Active pre-treatment with NRT while the smoker is still smoking can lead to a decrease in post-cessation withdrawal symptoms and an increase in sustained smoking cessation rates, while being safe [227, 228]. This approach is not yet widely used as the current labeling of the nicotine patch recommends using nicotine replacement therapy only after the quit date [228].

Bupropion

Bupropion is an antidepressant medication that can double the chances of long-term abstinence from smoking [229]. Its action in helping people to stop smoking is independent of its antidepressant effects, i.e. it works even in people without a history of depression. Like NRT, it leads to a reduction of the severity of withdrawal symptoms, but it may also have other actions that help people stop.

Bupropion acts by alleviating some of the symptoms of nicotine withdrawal, which include depression. Like NRT products and varenicline, bupropion has been endorsed by the US Clinical Practice Guideline as a first-line therapy [133].

The mechanism of action of bupropion is not fully understood, but some of its known actions are thought to contribute to its ability to help smokers quit [219]. These include inhibition of neuronal re-uptake of dopamine and noradrenalin, noncompetitive inhibition of the nicotinic acetylcholine receptor and effects on serotonin re-uptake. From a clinical perspective, bupropion helps smokers by reducing the severity of withdrawal symptoms, including the desire or urge to smoke, thereby making the quit attempt easier and success more likely [230].

Bupropion is equally effective for men and women [229]. It has also been shown that combining bupropion with NRT medications may increase cessation rates relative to bupropion alone [229].

- It is recommended that treatment is started while the patient is still smoking and a target quit date (TQD) set within the first 2 weeks of treatment with bupropion, preferably in the second week

- The initial dose is 150 mg to be taken daily for 6 days, increasing on Day 7 to 150 mg twice daily, keeping at least 8 hours between each dose. The maximum recommended dose of bupropion is 300 mg/day and the recommended treatment duration is 7–9 weeks

- Side effects of dry mouth and insomnia are the most common adverse events associated with use. At doses up to the maximum recommended daily dose, a small risk of seizures exists (approximately 0.1% or 1/1,000)

- The prescribing information for bupropion includes a Boxed Warning for severe neuropsychiatric events. Depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion for smoking cessation. The patient should stop taking bupropion and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical are observed, or if the patient develops suicidal ideation or suicidal behavior. Ongoing monitoring and supportive care should be provided until neuropsychiatric symptoms resolve

- All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases

- Use of bupropion as a smoking cessation therapy in patients under 18 years of age is not

recommended as the safety and efficacy have not been evaluated in these subjects

- Bupropion and its metabolites are excreted in human breast milk. A decision on whether to abstain from breast-feeding or to abstain from therapy with bupropion should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of bupropion therapy to the mother

- Bupropion should be used with extreme caution in patients with severe hepatic cirrhosis, where a reduced frequency of dosing is required. In patients with hepatic impairment (including mild-to-moderate hepatic cirrhosis), bupropion should be used with caution and a reduced frequency of dosing considered

- Bupropion is contraindicated in patients with a seizure disorder. Bupropion as a smoking cessation treatment (marketed by GlaxoSmithKline as Zyban®) is contraindicated in patients already being treated with this medicine (bupropion is approved for use as an oral antidepressant and is marketed by GlaxoSmithKline in immediate-, sustained- and/or extended-release formulations, as Wellbutrin®, Wellbutrin SR® and Wellbutrin XL®, respectively) or any other medications that contain bupropion because the incidence of seizure is dose-dependent

- Bupropion is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion

- Bupropion is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines)

- The concurrent administration of bupropion and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with bupropion

- Bupropion is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up bupropion [232]

Varenicline

Varenicline, a partial agonist of the α4-β2 nicotinic AChR, is the first non-nicotine compound specifically developed for smoking cessation [233]. It combines agonistic and antagonistic properties in one drug. As an agonist it reduces withdrawal symptoms, as antagonist it blocks the reward pathway after nicotine uptake. After oral intake it has a high absorption rate of 99% and a low protein binding capacity. It is not metabolized and has no interaction with cytochrome P450, but has a renal excretion rate of >90%. Varenicline has no relevant interaction with food or drugs [234].

Varenicline has consistently been shown to be the most effective pharmaceutical agent for smoking cessation [235]. Treatment with varenicline significantly increased, CO-confirmed 4-week continuous quit rates (CQRs)/carbon monoxide (CO)-confirmed continuous abstinence rate (CARs) relative to rates for bupropion or placebo: CARs in Weeks 9 through 12 ranged from 43.9% (odds ratio [OR] = 3.85; $P<0.001$ *vs* placebo; OR = 1.90; $P<0.001$ *vs* bupropion SR) to 65.4% (OR = 2.98; $P<0.001$ *vs* placebo). In head-to-head studies, treatment with varenicline has resulted in higher cessation rates than bupropion SR [236, 237]. Varenicline is also efficacious and well tolerated in patients with cardiovascular disease (CVD) [238] and mild-to-moderate COPD [239]. The clinical trial in patients with CVD showed that varenicline was effective, well tolerated and did not increase cardiovascular events or mortality. However, the trial size and duration limit definitive conclusions about safety [238]. A recent 12-week placebo-controlled study conducted in selected countries in Latin America, Africa, and the Middle East found that treatment with varenicline (1 mg BID) significantly increased the CO-confirmed CAR in patients who were motivated to stop smoking. CAR at Weeks 9–12 was 53.6% *vs*

18.7% for the placebo group; OR = 5.8. This rate was maintained during Weeks 9–24 (39.7% *vs* 13.1%; OR = 4.8) [240].

- Varenicline treatment is initiated 1–2 weeks before TQD. Days 1–3: 0.5 mg in the morning after breakfast. Days 4–7: 0.5 mg twice daily, morning and evening daily after meals. Day 8 to end of treatment: 1 mg twice daily after meals. The tablets are swallowed whole with water. Treatment is continued for 12 weeks [241]

- For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks' treatment with varenicline at 1 mg twice daily may be considered [242, 243]

- Side effects including nausea, increased appetite, abnormal dreams, insomnia, headache, abdominal pain, constipation, dry mouth, dyspepsia, flatulence and vomiting are the most common adverse events associated with use

- Nausea is the most common side effect (28.6%) and is usually transitory and dose-dependent. Nausea leads to treatment discontinuation in less than 3%, and can usually be managed by temporary reduction of the dose and ensuring that each dose is taken with food and a glass of water [244]

- Changes in behavior or thinking, anxiety, psychosis, mood swings, aggressive behavior, depression, suicidal ideation and behavior, and suicide attempts have been reported in patients attempting to quit smoking with varenicline in the post-marketing experience [241]. Warnings regarding these events have been added to the product label. According to the label, patients experiencing neuropsychiatric symptoms while on varenicline should discontinue this medication and immediately consult their doctor. An increase in neuropsychiatric events, with the exception of sleep disorders, has not been found in randomized, placebo-controlled varenicline trials [245]. These trials however excluded patients with psychiatric disorders (except depression that did not require treatment in the previous 12 months). Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness

- A recent meta-analysis of 14 double-blind randomized controlled trials for varenicline concluded that this drug was associated with a significantly increased risk of serious adverse cardiovascular events compared with placebo (1.06% [52/4908] *vs* 0.82% [27/3308]) [246]. Limitations of the meta-analysis have been highlighted by the editorial accompanying the publication [247] and letters to the journal's editor [248]. The European Medicines Agency (EMA) has also posted an evaluation of the results, including a number of methodological limitations or deficiencies for this meta-analysis due to "the low number of events seen, the types of events counted, the higher drop-out rates in people receiving placebo, the lack of information on the timing of events, and the exclusion of studies in which no-one had an event" [249]. The EMA worked with the marketing authorization holder of varenicline, to include more information on cardiovascular events in the medicine's product information. More information and a warning about certain cardiovascular events occurring at a higher rate in the varenicline *vs* placebo arms in the cardiovascular study [238] were also added. Pfizer (which markets the drug) subsequently reported that the company is working with the US FDA to independently conduct a meta-analysis. This meta-analysis will address a number of limitations in the above mentioned meta-analysis. Pfizer expects that it will be based on a more reliable composite endpoint to measure cardiovascular risk, as well as a validated process to classify, or adjudicate, cardiovascular events that are part of the composite endpoint. The company plans to publicly disclose the results when this analysis is completed [248]

- Use of varenicline as a smoking cessation therapy in patients under 18 years of age is not recommended as the safety and efficacy have not been evaluated in these subjects

- Patients who are pregnant or breast-feeding or planning to become pregnant should be advised of: the risks of smoking to a pregnant mother and her developing baby, the potential risks of varenicline use during pregnancy and breast-feeding, and the benefits of smoking cessation with and without varenicline

- Varenicline is contraindicated in patients with a known history of serious hypersensitivity reactions or skin reactions to the drug [241]

Second-line medications

Besides the first-line medications already discussed (NRT products, bupropion, and vareniciline), nortriptyline and clonidine are endorsed as second-line therapies by the current US Clinical Practice Guideline [133].

Nortriptyline

Nortriptyline is a tricyclic antidepressant that has been shown to be as effective as bupropion and NRT in aiding smoking cessation [250, 251]. Its action in helping people to stop smoking is independent of its antidepressant effects, and it works in those without a history of depression. Combining nortriptyline with NRT has not been demonstrated to provide greater efficacy than either agent alone. A US study found that this combination increased the cessation rate with little effect on withdrawal symptoms [252]. However, a subsequent UK study found that nortriptyline in combination with NRT was less effective than either agent given alone [253]. The main advantages of nortriptyline are its low cost and the ability to monitor therapeutic blood levels.

- Dosage: initially 25 mg/day, begin 10–28 days before TQD. Increase dose gradually to 25 mg taken 3–4 times daily (75–100 mg/day) over 10 days to 5 weeks. Continue for a total of 12 weeks. The dose should be tapered at the end of treatment to avoid withdrawal symptoms that may occur if it is stopped abruptly. There is limited evidence of any benefits of extending treatment past 3 months [135]

- Side effects include fast heart rate, blurred vision, urinary retention, dry mouth, constipation, weight gain or loss, and low blood pressure on standing [219]

Clonidine

Clonidine is an a-2-noradrenergic agonist used in the treatment of hypertension [219]. It has been shown to diminish symptoms of both opiate and alcohol withdrawal symptoms. In one study of heavy smokers who had failed in previous quit attempts it showed that those treated with clonidine had twice the rate of abstinence as those treated with placebo at the end of the 4-week treatment, and the effect persisted for the 6-month follow-up period.

- Dosage is 100 μg twice daily (oral or the equivalent transdermal patch), titrated up to a maximum of 400 μg per day, as tolerated. If clonidine therapy is planned prior to the TQD it should be commenced 48–72 hours before smoking cessation. This will allow time for steady state plasma concentrations to be reached before the onset of tobacco withdrawal symptoms [254]

- Side effects include dry mouth, drowsiness, dizziness, sedation, and constipation

- As clonidine is an antihypertensive medication, clinicians should monitor blood pressure in patients using this drug [133]

Combination treatments

Combining a nicotine patch with a rapid delivery form of NRT is more effective than a single type of NRT for helping people quit smoking [205]. There are currently limited data for other approaches combining NRT with non-NRT medications, e.g. NRT plus bupropion [231], NRT plus varenicline [255], and bupropion plus varenicline [256]. Such combination therapy may increase abstinence rates compared with monotherapy [257] and should be considered along with non-pharmacological support for patients who are struggling to cope with withdrawal symptoms and are at risk of abandoning their quit attempt.

First-line Pharmacotherapy	Dosage	Duration	Availability
Sustained release bupropion hydrochloride	150 mg every morning for 3 days, then 150 mg twice daily (begin treatment 1–2 weeks pre-quit)	7–12 weeks Maintenance up to 6 months	Prescription only
Nicotine gum	In patients who have been smoking 1–24 cigarettes/day: 2 mg gum (up to 24 pieces/day); in patients who have been smoking ≥25 cigarettes/day: 4 mg gum (up to 24 pieces/day)	Up to 12 weeks	OTC only
Nicotine inhaler	6–16 cartridges/day	Up to 6 months	Prescription only
Nicotine lozenge	If time to first cigarette smoked each day is >30 mins: 2 mg lozenge; if the time to first cigarette smoked each day is ≤30 mins: 4 mg lozenge. Between 4–20 lozenges/day	Up to 12 weeks	OTC only
Nicotine nasal spray	8–40 doses/day	3–6 months	Prescription only
Nicotine patch	Step-down dosage from 21 mg/24 hrs for 4 weeks, then 14 mg/24 hrs for 2 weeks, then 7 mg/24 hrs for 2 weeks	Up to 8 weeks	Prescription and OTC
Varenicline	0.5 mg/day for 3 days, 0.5 mg twice/day for 4 days, then 1 mg twice/day (begin treatment 1 week prequit)	3–6 months	Prescription only

Notes: OTC, over the counter; *The information contained in this table is not comprehensive; please refer to package inserts for additional information including safety information for your country.

Table 11: Suggestions for the clinical use of pharmacotherapies for smoking cessation* (adapted from US Public Health Service guidelines 2008) [133]

Medication	Number of arms*	Estimated odds ratio (95% confidence interval)	Estimated abstinence rate (95% confidence interval)
Placebo	80	1.0	13.8
Monotherapies			
Varenicline (2 mg/day)	5	3.1 (2.5, 3.8)	33.2 (28.9, 37.8)
Nicotine nasal spray	4	2.3 (1.7, 3.0)	26.7 (21.5, 32.7)
High dose nicotine patch (>25 mg) (these included both standard or long-term duration)	4	2.3 (1.7, 3.0)	26.5 (21.3, 32.5)
Long-term nicotine gum (>14 weeks)	6	2.2 (1.5, 3.2)	26.1 (19.7, 33.6)
Varenicline (1 mg/day)	3	2.1 (1.5, 3.0)	25.4 (19.6, 32.2)
Nicotine inhaler	6	2.1 (1.5, 2.9)	24.8 (19.1, 31.6)
Clonidine	3	2.1 (1.2, 3.7)	25.0 (15.7, 37.3)
Bupropion SR	26	2.0 (1.8, 2.2)	24.2 (22.2, 26.4)
Nicotine patch (6–14 weeks)	32	1.9 (1.7, 2.2)	23.4 (21.3, 25.8)
Long-term nicotine patch (>14 weeks)	10	1.9 (1.7, 2.3)	23.7 (21.0, 26.6)
Nortriptyline	5	1.8 (1.3, 2.6)	22.5 (16.8, 29.4)
Nicotine gum (6–14 weeks)	15	1.5 (1.2, 1.7)	19.0 (16.5, 21.9)
Combination therapies			
Patch (long-term; >14 weeks) + ad lib NRT (gum or spray)	3	3.6 (2.5, 5.2)	36.5 (28.6, 45.3)
Patch + bupropion SR	3	2.5 (1.9, 3.4)	28.9 (23.5, 35.1)
Patch + nortriptyline	2	2.3 (1.3, 4.2)	27.3 (17.2, 40.4)
Patch + inhaler	2	2.2 (1.3, 3.6)	25.8 (17.4, 36.5)
Patch + second generation antidepressants (paroxetine, venlafaxine)	3	2.0 (1.2, 3.4)	24.3 (16.1, 35.0)
Medications not shown to be effective			
Selective serotonin re-uptake inhibitors (SSRIs)	3	1.0 (0.7, 1.4)	13.7 (10.2, 18.0)
Naltrexone	2	0.5 (0.2, 1.2)	7.3 (3.1, 16.2)

*The information contained in this table is not comprehensive; please refer to package inserts for additional information including safety information. Reproduced with permission from the 2008 US guidelines [133]

Table 12: Effectiveness and abstinence rates for various medications and medication combinations compared to placebo at 6-months post-quit (*n*=86 studies) [133]

Country	Medication	Formulation	Brandname(s)	Route of Application	Cost (USD)	Coverage Subsidy
South Africa	NRT	Gum 2, 4 mg	Nicorette	oral	-	No
	NRT	Patch 5, 10, 15 mg	Nicorette	transdermal	-	No
	NRT	Lozenges 1 mg	Nicorette	sublingual	-	No
	NRT	Tablets 2 mg	Nicorette	oral	-	No
	NRT	Mouth spray 0.33–1 mg	Quit	oral	-	No
	Bupropion	Tablets 150 mg	Zyban	oral	-	No
	Varenicline	Tablets 0.5, 1 mg	Champix	oral	-	No
Egypt	Varenicline	Tablets 0.5, 1 mg	Champix	oral	-	-
	NRT	Patch	-		-	-
Jordan	NRT	Inhaler	-	oral	-	-
	Varenicline	Tablet	Champix	oral	-	-
UAE	NRT	Gum 2, 4 mg	Nicotinell	oral	-	-
	NRT	Lozenges 2, 4 mg	-	oral	-	-
	NRT	Patch 7, 14, 21 mg	Nicotinell	transdermal	-	-
	NRT	Inhaler 6–16 cartridges	-	oral	-	-
	Bupropion	Tablet 150 mg	Zyban	oral	-	-
	Varenicline	Tablet	Champix	oral	-	-
Lebanon	NRT	Gum 2, 4 mg	Nicorette	oral	-	-
	NRT	Patch	Nicorette	transdermal	-	-
	Varenicline	Tablet 0.5, 1 mg	Champix	oral	-	
	Bupropion	Tablet 150 mg	Zyban	oral	-	-
Saudi Arabia	NRT	Lozenge 1 mg	Nicotinell	sublingual	-	-
	NRT	Patch 7, 14, 21 mg	Nicoderm-CQ	transdermal	-	-
	Varenicline	Tablet 0.5, 1 mg	Champix	oral	-	-

Note: It is important that all countries in Africa and the Middle East should make these drugs available, accessible and affordable for smokers and proactively establish specialized centers for addiction management and cessation.

Table 13: Pharmacological treatments for smoking cessation available in Africa and the Middle East (countries with available data)

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References

1. The Tobacco Atlas. Third edition. Georgia, GA, The American Cancer Society; New York, NY, The World Lung Foundation. 2009. Available from: http://www.tobaccoatlas.org/ (accessed December 2011).

2. Coalición Latinoamericana de Profesionales de la Salud para el Tratamiento de la Dependencia al Tabaco. Actualizaciones Latinoamericanas sobre prevención y tratamiento del tabaquismo. 2010. Available from: http://www.asat.org.ar/novedades.php (accessed December 2011).

3. World Health Organization. Report on the global tobacco epidemic, 2008: The MPOWER package. Geneva, World Health Organization. 2008. Available from: http://whqlibdoc.who.int/publications/2008/9789241596282_eng.pdf (accessed December 2011).

4. World Health Organization. International statistical classification of diseases and related health problems 10th Revision, Version for 2010. Available from: http://apps.who.int/classifications/apps/icd/icd10online/ (accessed December 2011).

5. World Health Organization. WHO framework convention on tobacco control 2003. Geneva, World Health Organization. 2003. Available from: http://whqlibdoc.who.int/publications/2003/9241591013.pdf (accessed December 2011).

6. World Health Organization. The global burden of disease, 2004 update. Geneva, World Health Organization. 2008. Available from: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf (accessed December 2011).

7. Mackay J, Crofton J. Tobacco and the developing world. Br Med Bull. 1996; 52(1):206–21.

8. Guindon EG, Boisclair D. Past, current and future trends in tobacco use. Washington DC, The International Bank for Reconstruction and Development / The World Bank. 2003. Available from: http://www.worldbank.org/ (accessed December 2011).

9. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. Lancet Oncol. 2008; 9(7):667–75.

10. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol. 2009; 49:57–71. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2946180/ (accessed December 2011).

11. Arib O, Rat P, Molimard R, Chait A, Faure P, de Beaurepaire R. Electrophysiological characterization of harmane-induced activation of mesolimbic dopamine neurons. Eur J Pharmacol. 2010; 629(1–3):47–52.

12. Li MD. The genetics of smoking related behavior: a brief review. Am J Med Sci. 2003; 326(4):168–73.

13. Hamdani N, Ades J, Gorwood P. Heritability and candidate genes in tobacco use. Encephale. 2006; 32(6 Pt 1):966–75.

14. Tobacco and Genetics Consortium (TGC). Genome-wide meta-analyses identify multiple loci associated with smoking behavior. Nat Genet. 2010; 42(5):441–7.

15. Shafey O, Dolwick S, Guindon GE (eds). Tobacco Control Country Profiles 2003. American Cancer Society, Atlanta, GA. 2003. Available from: http://www.who.int/tobacco/global_data/country_profiles/en/index.html (accessed December 2011).

16. Lopez AD, Collishaw NE, Piha T. A descriptive model of cigarette epidemic in developed countries. Tob Control. 1994; 3:242–7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1759359/ (accessed December 2011).

17. Bolliger C, Fagerström KO. The tobacco epidemic. In: The Tobacco Epidemic. Progress in Respiratory Research. Bolliger C, Fagerstrom KO (eds), S. Kager AG, Basel. 1997.

18. Degenhardt L, Chiu W-T, Sampson N, *et al.* Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO world mental health surveys. PLoS Med. 2008; 5(7): e141. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2443200 (accessed December 2011).

19. Nakkash R, Lee K. The tobacco industry's thwarting of marketing restrictions and health warnings in Lebanon. Tob Control. 2009; 18(4):310–6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2709907/ (accessed December 2011).

20. Mamudu HM, Hammond R, Glantz SA. Project Cerberus: tobacco industry strategy to create an alternative to the Framework Convention on Tobacco Control. Am J Public Health. 2008; 98(9):1630–42. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2509616/ (accessed December 2011).

21. Patel P, Collin J, Gilmore AB. "The law was actually drafted by us but the Government is to be congratulated on its wise actions": British American Tobacco and public policy in Kenya. Tob Control. 2007; 16(1):1–8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2598451/ (accessed December 2011).

22. Hammond R, White C. The voice of truth, Volume 1: Multinational tobacco industry activity in the Middle East: a review of internal industry documents. Cairo, Egypt, World Health Organization, Regional Office for the Eastern Mediterranean. 2000. Available from: http://www.who.int/tobacco/policy/en/vot1_en.pdf (accessed December 2011).

23. LeGresley E, Lee K, Muggli ME, Patel P, Collin J, Hurt RD. British American Tobacco and the "insidious impact of illicit trade" in cigarettes across Africa. Tob Control. 2008; 17(5):339–46. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2602753 (accessed December 2011).

24. International Trade Centre website. Exports 2001–2010. International Trade in Goods Statistics by Product Group: 2401: Unmanufactured tobacco; tobacco refuse. Available at: http://www.intracen.org/tradstat/sitc3-3d/indexpe.htm (accessed December 2011).

25. FAO (Food and Agriculture Organization of the United Nations) website. FAOSTAT database; Trade: Commodities by country and Countries by commodity (2009 data). Available at: http://faostat.fao.org/site/342/default.aspx (accessed December 2011).

26. Samet JM, Yoon S-Y (eds). Chapter 3. Prevalence of tobacco use and factors Influencing initiation and maintenance among women. In: Gender, Women, and the Tobacco Epidemic. Geneva, World Health Organization. 2010. Available from: http://www.who.int/tobacco/publications/gender/women_tob_epidemic/en/index.html (accessed December 2011).

27. Shafey O. Health issues in the Arab American community. Global epidemiology and health hazards of tobacco use: Arab world patterns. Ethn Dis. 2007; 17(2 Suppl 3):S3-13–5.

28. Dar-Odeh NS, Bakri FG, Al-Omiri MK, *et al.* Narghile (water pipe) smoking among university students in Jordan: prevalence, pattern and beliefs. Harm Reduct J. 2010; 7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893172 (accessed March 2011).

29. Maziak W, Eissenberg T, Rastam S, *et al.* Beliefs and attitudes related to narghile (waterpipe) smoking among university students in Syria. Ann Epidemiol. 2004; 14(9):646–54.

30. Tamim H, Terro A, Kassem H, *et al.* Tobacco use by university students, Lebanon, 2001. Addiction. 2003; 98(7):933–9.

31. Ali AA. Histopathologic changes in oral mucosa of Yemenis addicted to water-pipe and cigarette smoking in addition to takhzeen al-qat. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007; 103(3):e55–9.

32. Zahran F, Yousef AA, Baig MH. A study of carboxyhaemoglobin levels of cigarette and sheesha smokers in Saudi Arabia. Am J Public Health. 1982; 72(7):722–4. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1650155 (accessed December 2011).

33. Al-Fayez SF, Salleh M, Ardawi M, Zahran FM. Effects of sheesha and cigarette smoking on pulmonary function of Saudi males and females. Trop Geogr Med. 1988; 40:115–23.

34. Bedwani R, el-Khwasky F, Renganathan E, *et al.* Epidemiology of bladder cancer in Alexandria, Egypt: tobacco smoking. Int J Cancer. 1997; 73:64–7.

35. Maziak W. Commentary: the waterpipe - a global epidemic or a passing fad. Int J Epidemiol. 2010; 39(3):857–9.

36. Martinasek MP, McDermott RJ, Martini L. Waterpipe (hookah) tobacco smoking among youth. Curr Probl Pediatr Adolesc Health Care. 2011; 41(2):34–57.

37. Jackson D, Aveyard P. Waterpipe smoking in students: prevalence, risk factors, symptoms of addiction, and smoke intake. Evidence from one British university. BMC Public Health. 2008; 8:174. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2413225 (accessed December 2011).

38. Maziak W. The global epidemic of waterpipe smoking. Addict Behav. 2011; 36(1–2):1–5.

39. Weglicki LS, Templin TN, Rice VH, Jamil H, Hammad A. Comparison of cigarette and water-pipe smoking by Arab and non-Arab-American youth. Am J Prev Med. 2008; 35(4):334–9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2575814 (accessed December 2011).

40. Dugas E, Tremblay M, Low NC, Cournoyer D, O'Loughlin J. Water-pipe smoking among North American youths. Pediatrics. 2010; 125(6):1184–9. Available from: http://pediatrics.aappublications.org/cgi/reprint/125/6/1184 (accessed December 2011).

41. Akl EA, Gaddam S, Gunukula SK, Honeine R, Jaoude PA, Irani J. The effects of waterpipe tobacco smoking on health outcomes: a systematic review. Int J Epidemiol. 2010; 39(3):834–57.

42. World Health Organization Study Group on Tobacco Product Regulation (TobReg). Waterpipe tobacco smoking: health effects, research needs and recommended actions by regulators. Geneva, World Health Organization. 2005. Available from: http://www.who.int/tobacco/global_interaction/tobreg/Waterpipe%20recommendation_Final.pdf (accessed December 2011).

43. Ward KD, Eissenberg T, Rastam S, *et al.* The tobacco epidemic in Syria. Tob Control. 2006; 15(Suppl 1):i24–9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2563543/ (accessed December 2011).

44. Al-Kuwari MG. Tobacco control in Qatar. Middle East J Fam Med. 2008; 6(6):11–3. Available from: http://www.mejfm.com/mejfmAug08_vol6-iss6/MEJFM_Vol6_Iss6.pdf (accessed December 2011).

45. Obot IS. The use of tobacco products among Nigerian adults: a general population survey. Drug Alcohol Depend. 1990; 26(2):203–8.

46. Desalu OO, Olokoba A, Danburam A, Salawu F, Issa B. Epidemiology of tobacco smoking among adults population in north-east Nigeria . Internet J Epidem. 2008; 6(1). Available from: http://www.ispub.com/journal/the_internet_journal_of_epidemiology/volume_6_number_1_8/article_printable/epidemiology_of_tobacco_smoking_among_adults_population_in_north_east_nigeria.html (accessed December 2011).

47. Samet JM, Yoon S-Y (eds). Chapter 6. The Marketing of Tobacco to Women: Global Perspectives. In: Gender, Women, and the Tobacco Epidemic. Geneva, World Health Organization. 2010. Available from: http://www.who.int/tobacco/publications/gender/women_tob_epidemic/en/index.html (accessed December 2011).

48. International Development Research Centre (IDRC). African Tobacco Situational Analysis (ATSA) website. Available at: http://atsa.atcri.org/ (accessed December 2011).

49. Titeca K, Joossens L, Raw M. Blood cigarettes: cigarette smuggling and war economies in central and eastern Africa. Tob Control. 2011; 20(3):226–32.

50. Peltzer K. Smokeless tobacco use among urban white and black South Africans. Psychol Rep. 1999; 85 (3 Pt 1):933–4.

51. Ayo-Yusuf OA, van Wyk C, van Wyk CW, de Wet I. Smokeless tobacco products on the South African market do not inhibit oral bacterial flora: a pilot study. South Afr J Epemiol Infect. 2005; 20(4):136–9. Available from: http://www.sajei.co.za/index.php/SAJEI/article/viewFile/28/24 (accessed December 2011).

52. Idris AM, Ibrahim YE, Warnakulasuriya KA, Cooper DJ, Johnson NW, Nilsen R. Toombak use and cigarette smoking in the Sudan: estimates of prevalence in the Nile state. Prev Med. 1998; 27(4):597–603.

53. Rudatsikira E, Muula AS, Siziya S. Current use of smokeless tobacco among adolescents in the Republic of Congo. BMC Public Health. 2010; 10:16. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2820474 (accessed December 2011).

54. Africa Tobacco Control Resource Centre (ATCRC). ATCRC website, Country Profile: South Africa. Available at: http://www.africatobaccocontrol.org/en/country_profile.php?country=South Africa&item=74 (accessed December 2011).

55. Smith DR, Leggat PA. An international review of tobacco smoking among medical students. J Postgrad Med. 2007; 53(1):55–62. Available from: http://www.jpgmonline.com/article.asp?issn=0022-3859;year=2007;volume=53;issue=1;spage=55;epage=62;aulast=Smith (accessed December 2011).

56. Tessier JF, Nejjari C, Bennani-Othmani M. Smoking in Mediterranean countries: Europe, North Africa and the Middle-East. Results from a co-operative study. Int J Tuberc Lung Dis. 1999; 3(10):927–37.

57. Richmond RL, Debono DS, Larcos D, Kehoe L. Worldwide survey of education on tobacco in medical schools. Tob Control. 1998; 7(3):247–52. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1763901 (accessed December 2011).

58. Richmond R (ed). Educating medical students about tobacco: planning and implementation. Paris: International Union Against Tuberculosis and Lung Disease, 1997. ISBN 0646314971.

59. Richmond R. Teaching medical students about tobacco. Thorax. 1999; 54(1):70–8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1745356 (accessed December 2011).

60. Oberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet. 2011; 377(9760):139–46.

61. World Health Organization. Tobacco: deadly in any form or disguise. Geneva, World Health Organization. 2006. Available from: www.who.int/tobacco/communications/events/wntd/2006/Tfi_Rapport.pdf (accessed December 2011).

62. Leonardi-Bee J, Smyth A, Britton J, Coleman T. Environmental tobacco smoke and fetal health: systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2008; 93(5):F351–61.

63. Kuschner WG, Reddy S, Mehrotra N, Paintal HS. Electronic cigarettes and third hand tobacco smoke: two emerging health care challenges for the primary care provider. Int J Gen Med. 2011; 4:115–20.

64. Global Youth Tobacco Survey Collaborative Group. Tobacco use among youth: a cross country comparison. Tob Control. 2002; 11(3):252–70. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1759013 (accessed December 2011).

65. Warren CW, Lea V, Lee J, Jones NR, Asma S, McKenna M. Change in tobacco use among 13–15 year olds between 1999 and 2008: findings from the Global Youth Tobacco Survey. Glob Health Promot. 2009; 16(2 Suppl):38–90. Available from: http://ped.sagepub.com/content/16/2_suppl/38.full.pdf+html (accessed December 2011).

66. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004; 328(7455):1519. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC437139 (accessed December 2011).

67. Ezzati M, Lopez AD. Regional, disease specific patterns of smoking-attributable mortality in 2000. Tob Control. 2004; 13(4):388–95. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1747946 (accessed December 2011).

68. World Health Organization. The top ten causes of death, fact sheet No. 310. Geneva, World Health Organization. 2007. Available from: http://www.who.int/mediacentre/factsheets/fs310.pdf (accessed December 2011).

69. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004; 43(10):1731–7. Available from: http://content.onlinejacc.org/cgi/reprint/43/10/1731.pdf (accessed December 2011).

70. Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: results from the third National Health and Nutrition Examination Survey. PLoS Med. 2005; 2(6):e160. Available from: http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0020160 (accessed December 2011).

71. Slama K. Global perspective on tobacco control. Part I. The global state of the tobacco epidemic. Int J Tuberc Lung Dis. 2008; 12(1):3–7.

72. Buist AS, McBurnie MA, Vollmer WM, *et al.* International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007; 370(9589):741–50.

73. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS. Am J Respir Crit Care Med. 2000; 161(2 Pt 1):381–90. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The lung health study. Available from: http://ajrccm.atsjournals.org/cgi/content/full/161/2/381 (accessed December 2011).

74. van Zyl Smit RN, Pai M, Yew WW, *et al*. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respir J. 2010; 35(1):27–33.

75. Jones LL, Hashim A, McKeever T, Cook DG, Britton J, Leonardi-Bee J. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. Respir Res. 2011; 12:5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3022703 (accessed December 2011).

76. Abdallah FCB, Chermiti F, Taktak S, Chtourou A, Mahouachi R, Kheder AB. Burden of Chronic Respiratory Diseases (CRD) in Middle East and North Africa (MENA). World Allergy Org J. 2011; 4(1):S6–8. Available from: http://journals.lww.com/waojournal/Fulltext/2011/01001/Burden_of_Chronic_Respiratory_Diseases__CRD__in.2.aspx (accessed December 2011).

77. Boyle P. Cancer, cigarette smoking and premature death in Europe: a review including the Recommendations of European Cancer Experts Consensus Meeting, Helsinki, October 1996. Lung Cancer. 1997; 17(1):1–60.

78. Pfeifer GP, Denissenko MF, Olivier M, Tretyakova N, Hecht SS, Hainaut P. Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene. 2002; 21(48):7435–51. Available from: http://www.nature.com/onc/journal/v21/n48/pdf/1205803a.pdf (accessed December 2011).

79. Dey S, Soliman AS. Cancer in the global health era: opportunities for the Middle East and Asia. Asia Pac J Public Health. 2010; 22(3 Suppl):75S–82S.

80. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. CA Cancer J Clin. 2005; 55(2):74–108.

81. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010; 127(12):2893–917.

82. Al-Hamdan N, Al-Jarallah M, Al-Jarallah M, *et al*. The incidence of lung cancer in the Gulf Cooperation Council countries. Ann Saudi Med. 2006; 26(6):433-8. Available from: http://www.saudiannals.net/temp/AnnSaudiMed266433-4274494_115224.pdf (accessed December 2011).

83. Ibrahim WH, Rasul KI, Khinji A, Ahmed MS, Bener A. Clinical and epidemiological characteristics of lung cancer cases in Qatar. East Mediterr Health J. 2010; 16(2):166–70.

84. Ahmed HG, Mahgoob RM. Impact of Toombak dipping in the etiology of oral cancer: gender-exclusive hazard in the Sudan. J Cancer Res Ther. 2007; 3(2):127–30.

85. Feng BJ, Khyatti M, Ben-Ayoub W, *et al*. Cannabis, tobacco and domestic fumes intake are associated with nasopharyngeal carcinoma in North Africa. Br J Cancer. 2009; 101(7):1207–12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2768108 (accessed December 2011).

86. Sumeruk R, Segal I, Te Winkel W, van der Merwe CF. Oesophageal cancer in three regions of South Africa. S Afr Med J. 1992; 81(2):91–3.

87. Lingwood RJ, Boyle P, Milburn A, *et al*. The challenge of cancer control in Africa. Nat Rev Cancer. 2008; 8(5):398–403.

88. U.S. Department of Health and Human Services (US DHSS). The health consequences of smoking: Nicotine addiction. A report of the surgeon general. Department of Health and Human Services, Public Health Service. 1988. Available from: http://profiles.nlm.nih.gov/NN/B/B/Z/D/_/nnbbzd.pdf (accessed December 2011).

89. Benowitz NL. Nicotine addiction. N Engl J Med. 2010; 362(24):2295–303. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2928221/ (accessed December 2011).

90. Fakhfakh R, Aouina H, Gharbi L, *et al*. Smoking dependence and symptoms of anxiety and depression among Tunisian smokers. Rev Mal Respir. 2003; 20(6 Pt 1):850–7. Available from: http://www.em-consulte.com/article/143695 (accessed December 2011).

91. Maziak W, Rastam S, Ibrahim I, Ward KD, Shihadeh A, Eissenberg T. CO exposure, puff topography, and subjective effects in waterpipe tobacco smokers. Nicotine Tob Res. 2009; 11(7):806–11. Available from: http://www.em-consulte.com/article/143695 (accessed December 2011).

92. Weitzman M, Cook S, Auinger P, *et al*. Tobacco smoke exposure is associated with the metabolic syndrome in adolescents. Circulation. 2005; 112(6):862–9.

93. Xie B, Palmer PH, Pang Z, Sun P, Duan H, Johnson CA. Environmental tobacco use and indicators of metabolic syndrome in Chinese adults. Nicotine Tob Res. 2010; 12(3):198–206. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2825097 (accessed December 2011).

94. Xie XT, Liu Q, Wu J, Wakui M. Impact of cigarette smoking in type 2 diabetes development. Acta Pharmacol Sin. 2009; 30(6):784–7.

95. Bišanović S, Mehić B, Sivić S. Status of lipids and the frequency diseases of cardiovascular origin in smokers according to the length period of smoking and a number of cigarettes smoked daily. Bosn J Basic Med Sci. 2011; 11(1):46–51.

96. Unverdorben M, von Holt K, Winkelmann BR. Smoking and atherosclerotic cardiovascular disease: part II: role of cigarette smoking in cardiovascular disease development. Biomark Med. 2009; 3(5):617–53.

97. Heiss C, Amabile N, Lee AC, *et al*. Brief secondhand smoke exposure depresses endothelial progenitor cells activity and endothelial function: sustained vascular injury and blunted nitric oxide production. J Am Coll Cardiol. 2008; 51(18):1760–71. Available from: http://content.onlinejacc.org/cgi/reprint/51/18/1760.pdf (accessed December 2011).

98. Warnakulasuriya S, Dietrich T, Bornstein MM, *et al*. Oral health risks of tobacco use and effects of cessation. Int Dent J. 2010; 60(1):7–30.

99. Sham AS, Cheung LK, Jin LJ, Corbet EF. The effects of tobacco use on oral health. Hong Kong Med J. 2003; 9(4):271–7. Available from: http://www.hkmj.org/article_pdfs/hkm0308p271.pdf (accessed December 2011).

100. Steinberg MB, Schmelzer AC, Richardson DL, Foulds J. The case for treating tobacco dependence as a chronic disease. Ann Intern Med. 2008; 148(7):554–6.

101. Swart D, Panday S. WHO Tobacco control papers: the surveillance and monitoring of tobacco control in South Africa. Geneva, World Health Organization. 2003. Available from: http://www.who.int/tobacco/training/success_stories/en/best_practices_south_africa_surveillance.pdf (accessed December 2011).

102. Fadhil I. Tobacco control in Bahrain: an overview. Eastern Med Health J. 2007; 13(3):719–26. Available from: http://www.emro.who.int/emhj/1303/13_3_2007_719_726.pdf (accessed December 2011).

103. Luo Z, Alvarado GF, Hatsukami DK, Johnson EO, Bierut LJ, Breslau N. Race differences in nicotine dependence in the Collaborative Genetic study of Nicotine Dependence (COGEND). Nicotine Tob Res. 2008; 10(7):1223–30.

104. Shields AE, Levy DE, Blumenthal D, *et al*. Primary care physicians' willingness to offer a new genetic test to tailor smoking treatment, according to test characteristics. Nicotine Tob Res. 2008; 10(6):1037–45.

105. Viswanath K, Herbst RS, Land SR, *et al*. Tobacco and cancer: an American Association for Cancer Research policy statement. Cancer Res. 2010; 70(9):3419–30. Available from: http://cancerres.aacrjournals.org/content/70/9/3419.long (accessed December 2011).

106. World Health Organization. WHO framework Convention on Tobacco Control website: About WHO Framework Convention on Tobacco Control. 2011. Available at: http://www.who.int/fctc/en/ (accessed December 2011).

107. Leung CM-K, Leung AKC, Hon K-LE, Kong AY-F. Fighting tobacco smoking – a difficult but not impossible battle. Int J Environ Res Public Health. 2009; 6:69–83. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2672325/pdf/ijerph-06-00069.pdf (accessed December 2011).

108. Jha P, Chaloupka FJ, Moore J, *et al*. Chapter 46: Tobacco addiction. In: Jamison DT, Breman JG, Measham AR, *et al*. (eds). Disease Control Priorities in Developing Countries. 2nd edition. Washington (DC): World Bank; 2006. Available from: http://www.ncbi.nlm.nih.gov/books/NBK11741/ (accessed December 2011).

109. World Bank. Tobacco control: at a glance, Washington DC. 2003. Available from: http://siteresources.worldbank.org/INTPHAAG/Resources/AAGTobacControlEngv46-03.pdf (accessed December 2011).

110. Jha P, Chaloupka FJ. Curbing the epidemic: governments and the economics of tobacco control. Washington, World Bank. 1999. Available from: http://www.usaid.gov/policy/ads/200/tobacco.pdf (accessed December 2011).

111. van Walbeek C. The economics of tobacco control in South Africa [PhD thesis]: University of Cape Town; 2005. Available from: http://www.commerce.uct.ac.za/economics/staff/cwalbeek/research.asp (accessed December 2011).

112. Blecher E. Targeting the affordability of cigarettes: a new benchmark for taxation policy in low-income and-middle-income countries. Tob Control. 2010; 19(4):325–30.

113. Hu TW, Mao Z, Liu Y, de Beyer J, Ong M. Smoking, standard of living, and poverty in China. Tob Control. 2005; 14(4):247–50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1748057 (accessed December 2011).

114. McNabola A, Gill LW. The control of environmental tobacco smoke: a policy review. Int J Environ Res Public Health. 2009; 6(2):741–58. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2672352/pdf/ijerph-06-00741.pdf (accessed December 2011).

115. Callinan JE, Clarke A, Doherty K, Kelleher C. Legislative smoking bans for reducing second hand smoke exposure, smoking prevalence and tobacco consumption. Cochrane Database Syst Rev. 2010; 4:CD005992. Available from: http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD005992/pdf_fs.html (accessed December 2011).

116. Global Smokefree Partnership (GSP). Global voices report: rebutting the tobacco industry, winning smokefree air, 2009 Status Report. 2009. Available from: http://www.globalsmokefreepartnership.org/ficheiro/GV_report_09.pdf (accessed December 2011).

117. WHO Framework Convention on Tobacco Control (FCTC). FCTC website, News: General news: Nigerian Senate passes Tobacco Control Bill. 16 March 2011. Available from: http://www.fctc.org/ (accessed December 2011).

118. Saffer H, Chaloupka FJ. Tobacco Advertising: Economic Theory and International Evidence. NBER Working Paper Series. 1999; w6958. Available from: http://ssrn.com/abstract=160111 (accessed December 2011).

119. Blecher E. The impact of tobacco advertising bans on consumption in developing countries. J Health Econ. 2008; 27(4):930–42.

120. Dreeman B, Chapman S. British American Tobacco on Facebook: undermining Article 13 of the global World Health Organization framework convention on tobacco control. Tob Control. 2010; 19(3):e1–9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2989160 (accessed December 2011).

121. Hammond D, Fong GT, McNeill A, Borland R, Cummings KM. Effectiveness of cigarette warning labels in informing smokers about the risks of smoking: findings from the International Tobacco Control (ITC) four country survey. Tob Control. 2006; Suppl 3:iii19–25.

122. Mahood G. Canada's tobacco package label or warning system: "telling the truth" about tobacco product risks. Geneva, World Health Organization. 2003. Available from: http://www.who.int/tobacco/training/success_stories/en/best_practices_canada_package.pdf (accessed December 2011).

123. Borland R, Wilson N, Fong GT, *et al*. Impact of graphic and text warnings on cigarette packs: findings from four countries over five years. Tob Control. 2009; 18(5):358–64. Available from: http://tobaccocontrol.bmj.com/content/18/5/358.long (accessed December 2011).

124. Hammond D, Fong GT, Borland R, Cummings KM, McNeill A, Driezen P. Text and graphic warnings on cigarette packages: findings from the international tobacco control four country study. Am J Prev Med. 2007; 32(3):202–9.

125. Hammond D, Fong GT, McDonald PW, Brown KS, Cameron R. Graphic Canadian cigarette warning labels and adverse outcomes: evidence from Canadian smokers. Am J Public Health. 2004; 94(8):1442–5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1448469 (accessed December 2011).

126. Hammond D. "Plain packaging" regulations for tobacco products: the impact of standardizing the color and design of cigarette packs. Salud Publica Mex. 2010; 52(Suppl 2):S226–32.

127. Nakkash R, Khalil J. Health warning labelling practices on narghile (shisha, hookah) waterpipe tobacco products and related accessories. Tob Control. 2010; 19(3):235–9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2989164 (accessed December 2011).

128. Elton-Marshall T, Fong GT, Zanna MP, *et al*. Beliefs about the relative harm of "light" and "low tar" cigarettes: findings from the International Tobacco Control (ITC) China survey. Tob Control. 2010; 19(Suppl 2):i54–62.

129. Strasser AA, Lerman C, Sanborn PM, Pickworth WB, Feldman EA. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. Drug Alcohol Depend. 2007; 86(2–3):294–300.

130. Hammond, D, Wiebel F, Kozlowski LT, *et al*. Revising the machine smoking regime for cigarette emissions: implications for tobacco control policy. Tob Control. 2007; 16(1):8–14. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2598458/ (accessed December 2011).

131. Joossens L, Raw M. The Tobacco Control Scale: a new scale to measure country activity. Tob Control. 2006; 15(3):247–53. Available from: http://tobaccocontrol.bmj.com/content/15/3/247.long (accessed December 2011).

132. Joossens L, Raw M. Tobacco Control Scale 2010 in Europe. Brussels, Association of European Cancer Leagues. 2010. Available from: http://www.ensp.org/node/576 (accessed December 2011).

133. Fiore MC, Jaén CR, Baker TB, *et al*. Treating tobacco use and dependence: 2008 update. clinical practice guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. 2008. Available from: http://www.ncbi.nlm.nih.gov/books/NBK12193/ (accessed December 2011).

134. National Institute for Health and Clinical Excellence. Brief interventions and referral for smoking cessation in primary care and other settings. 2006. Available from: http://www.nice.org.uk/nicemedia/live/11375/31864/31864.pdf (accessed December 2011).

135. Department of Health, New Zealand. New Zealand smoking cessation guidelines. 2007. Available from: http://www.moh.govt.nz/moh.nsf/indexmh/nz-smoking-cessation-guidelines (accessed December 2011).

136. Smith SS, McCarthy DE, Japuntich SJ, *et al*. Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. Arch Intern Med. 2009; 169(22):2148–55.

137. American Cancer Society (ACS). Guide to quitting smoking. Last revised 31 January 2011. Available from: http://www.cancer.org/acs/groups/cid/documents/webcontent/002971-pdf.pdf (accessed December 2011).

138. Cahill K, Lancaster T, Green N. Stage-based interventions for smoking cessation (review). Cochrane Database Syst Rev. 2010; 11:CD004492. Available from: http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD004492/pdf_fs.html (accessed December 2011).

139. Norcross JC, Krebs PM, Prochaska JO. Stages of change. J Clin Psychol. 2011; 67(2):143–54. Available from: http://onlinelibrary.wiley.com/doi/10.1002/jclp.20758/pdf (accessed December 2011).

140. Litt J. How to provide effective smoking cessation advice in less than a minute without offending the patient. Aust Fam Physician. 2002; 31(12):1087–94.

141. McIvor A, Kayser J, Assaad JM, *et al*. Best practices for smoking cessation interventions in primary care. Can Respir J. 2009; 16(4):129–34.

142. Mottillo S, Filion KB, Bélisle P, *et al*. Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. Eur Heart J. 2009; 30(6):718–30.

143. Dickinson JA, Wiggers J, Leeder SR, Sanson-Fisher RW. General practitioners' detection of patients' smoking status. Med J Aust. 1989; 150(8):420–2,425–6.

144. Shipton D, Tappin DM, Vadiveloo T, Crossley JA, Aitken DA, Chalmers J. Reliability of self reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study. BMJ. 2009; 339:b4347. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2771076 (accessed December 2011).

145. 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(9):1119–27.

146. Fagerström KO. Determinants of tobacco use and renaming the FTND to the Fagerström Test for Cigarette Dependence. Nicotine Tob Res. 2012; 14(1):75–8.

147. Borland R, Yong HH, O'Connor RJ, Hyland A, Thompson ME. The reliability and predictive validity of the Heaviness of Smoking Index and its two components: findings from the International Tobacco Control four country study. Nicotine Tob Res. 2010; 12(Suppl):S45–50.

148. Salameh P, Waked M, Aoun Z. Waterpipe smoking: construction and validation of the Lebanon Waterpipe Dependence Scale (LWDS-11). Nicotine Tob Res. 2008; 10(1):149–58.

149. Akl EA, Aleem S, Gunukula SK, Honeine R, Abou Jaoude P, Irani J. Survey instruments used in clinical and epidemiological research on waterpipe tobacco smoking: a systematic review. BMC Public Health. 2010; 10:415. Available from: http://www.biomedcentral.com/content/pdf/1471-2458-10-415.pdf (accessed December 2011).

150. Young JM, Ward JE. Implementing guidelines for smoking cessation advice in Australian general practice: opinions, current practices, readiness to change and perceived barriers. Family Practice. 2001; 18(1):14–20. Available from: http://fampra.oxfordjournals.org/content/18/1/14.full (accessed December 2011).

151. Ferketich AK, Gallus S, Colombo P, *et al*. Physician-delivered advice to quit smoking among Italian smokers. Am J Prev Med. 2008; 35(1):60–3.

152. Hebert JR, Kristeller J, Ockene JK, *et al*. Patient characteristics and the effect of three physician-delivered smoking interventions. Prev Med. 1992; 21(5):557–73.

153. West R, Sohal T. "Catastrophic" pathways to smoking cessation: findings from national survey. BMJ. 2006; 332(7539):458–60. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1382540 (accessed December 2011).

154. Lindson N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. Cochrane Database Syst Rev. 2010; 3:CD008033.

155. Asfar T, Ebbert JO, Klesges RC, Relyea GE. Do smoking reduction interventions promote cessation in smokers not ready to quit? Addict Behav. 2011; 36(7):764–8.

156. Williamson DF, Madans J, Anda RF, Kleinman JC, Giovino GA, Byers T. Smoking cessation and severity of weight gain in a national cohort. N Engl J Med. 1991; 324(11):739–45. Available from: http://www.nejm.org/doi/full/10.1056/NEJM199103143241106 (accessed December 2011).

157. Flegal KM, Troiano RP, Pamuk ER, Kuczmarski RJ, Campbell SM. The influence of smoking cessation on the prevalence of overweight in the United States. N Engl J Med. 1995; 333(18):1165–70. Available from: http://www.nejm.org/doi/full/10.1056/NEJM199511023331801 (accessed December 2011).

158. Doherty K, Kinnunen T, Militello FS, Garvey AJ. Urges to smoke during the first month of abstinence: relationship to relapse and predictors. Psychopharmacology (Berl). 1995; 119(2):171–8.

159. Lai DT, Cahill K, Qin Y, Tang JL. Motivational interviewing for smoking cessation. Cochrane Database Syst Rev. 2010; 1:CD006936. Available from: http://www.thecochranelibrary.com/userfiles/ccoch/file/World%20No%20Tobacco%20Day/CD006936.pdf (accessed December 2011).

160. Fiore C, Cohen W, Cohen S. A clinical practice guideline for treating tobacco use and dependence: a US public health service report. The Tobacco use consortium representatives. JAMA. 2000; 283:3244–54.

161. Cinciripini PM, Lapitsky L, Seay S, Wallfisch A, Kitchens K, Van Vunakis H. The effects of smoking schedules on cessation outcome: can we improve on common methods of gradual and abrupt nicotine withdrawal? J Consult Clin Psychol. 1995; 63(3):388–99.

162. Le Houezec J, Säwe U. Smoking reduction and temporary abstinence: new approaches for smoking cessation. J Mal Vasc. 2003; 28(5):293–300.

163. Agboola SA, Coleman TJ, McNeill AD. Relapse prevention in UK Stop Smoking Services: a qualitative study of health professionals' views and beliefs. BMC Health Serv Res. 2009; 9:67. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2679004 (accessed December 2011).

164. Richmond RL, Kehoe L, de Almeida Neto AC. Three year continuous abstinence in a smoking cessation study using the nicotine transdermal patch. Heart. 1997; 78(6):617–8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1892325/pdf/v078p00617.pdf (accessed December 2011).

165. Tønnesen P. Smoking cessation: how compelling is the evidence? A review. Health Policy. 2009; 91(Suppl 1):S15–25.

166. Jepson RG, Harris FM, Platt S, Tannahill C. The effectiveness of interventions to change six health behaviours: a review of reviews. BMC Public Health. 2010; 10:538. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2944371 (accessed December 2011).

167. Stead LF, Perera R, Lancaster T. Telephone counselling for smoking cessation. Cochrane Database Syst Rev. 2006; 3:CD002850.

168. Graham AL, Cobb NK, Papandonatos GD, *et al*. A randomized trial of internet and telephone treatment for smoking cessation. Arch Intern Med. 2011; 171(1):46–53.

169. Abdullah AS, Lam TH, Chan SK, *et al*. Effectiveness of a mobile smoking cessation service in reaching elderly smokers and predictors of quitting. BMC Geriatr. 2008; 8:25. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2570661 (accessed December 2011).

170. White AR, Rampes H, Liu JP, Stead LF, Campbell J. Acupuncture and related interventions for smoking cessation. Cochrane Database of Syst Rev. 2011; 1:CD000009. Available from: http://www2.cochrane.org/reviews/en/ab000009.html (accessed December 2011).

171. Barnes J, Dong CY, McRobbie H, Walker N, Mehta M, Stead LF. Hypnotherapy for smoking cessation. Cochrane Database Syst Rev. 2010; 10:CD001008. Available from: http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD001008/frame.html (accessed December 2011).

172. Memorial Sloan-Kettering Cancer Center. Smoking cessation: tools & techniques. Last updated July 2003. Available from: http://www.mskcc.org/mskcc/html/2546.cfm (accessed December 2011).

173. Stillman RJ, Rosenberg MJ, Sachs BP. Smoking and reproduction. Fertil Steril. 1986; 46(4):545–66.

174. Holloway AC, Kellenberger LD, Petrik JJ. Fetal and neonatal exposure to nicotine disrupts ovarian function and fertility in adult female rats. Endocrine. 2006; 30(2):213–6.

175. Knoll M, Talbot P. Cigarette smoke inhibits oocyte cumulus complex pick-up by the oviduct in vitro independent of ciliary beat frequency. Reprod Toxicol. 1998; 12(1):57–68.

176. Aliyu MH, Lynch O, 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.

177. Jauniaux E, Burton GJ. Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit. Early Hum Dev. 2007; 83(11):699–706.

178. Delpisheh A, Brabin L, Brabin BJ. Pregnancy, smoking and birth outcomes. Womens Health (Lond Engl). 2006; 2(3):389–403.

179. Wisborg K, Henriksen TB, Obel C, Skajaa E, Ostergaard JR. Smoking during pregnancy and hospitalization of the child. Pediatrics. 1999; 104(4):e46.

180. Pinho AP, Nunes ML. Epidemiological profile and strategies for diagnosing SIDS in a developing country: a case-control study. J Pediatr (Rio J). 2011; 87(2):115–22.

181. Obel C, Linnet KM, Henriksen TB, *et al.* Smoking during pregnancy and hyperactivity-inattention in the offspring – comparing results from three Nordic cohorts. Int J Epidemiol. 2009; 38(3):698–705. Available from: http://ije.oxfordjournals.org/content/38/3/698.long (accessed December 2011).

182. Vio F, Salazar G, Infante C. Smoking during pregnancy and lactation and its effects on breast-milk volume. Am J Clin Nutr. 1991; 54(6):1011–6. Available from: http://www.ajcn.org/content/54/6/1011.long (accessed December 2011).

183. Ratner PA, Johnson JL, Bottorff JL. Smoking relapse and early weaning among postpartum women: is there an association? Birth. 1999; 26(2):76–82.

184. Dahlström A, Ebersjö C, Lundell B. Nicotine exposure in breastfed infants. Acta Paediatr. 2004; 93(6):810–6.

185. Dorea JG. Maternal smoking and infant feeding: breastfeeding is better and safer. Matern Child Health J. 2007; 11(3):287–91.

186. Kendzor DE, Businelle MS, Costello TJ, *et al.* Breast feeding is associated with postpartum smoking abstinence among women who quit smoking due to pregnancy. Nicotine Tob Res. 2010; 12(10):983–8.

187. Hitsman B, Moss TG, Montoya ID, George TP. Treatment of tobacco dependence in mental health and addictive disorders. Can J Psychiatry. 2009; 54(6):368–78.

188. Dome P, Lazary J, Kalapos MP, Rihmer Z. Smoking, nicotine and neuropsychiatric disorders. Neurosci Biobehav Rev. 2010; 34(3):295–342.

189. Lawrence D, Mitrou F, Zubrick SR. Smoking and mental illness: results from population surveys in Australia and the United States. BMC Public Health. 2009; 9:285. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2734850 (accessed December 2011).

190. Cosci F, Knuts IJ, Abrams K, Griez EJ, Schruers KR. Cigarette smoking and panic: a critical review of the literature. J Clin Psychiatry. 2010; 71(5):606–15.

191. Hall SM. Nicotine interventions with comorbid populations. Am J Prev Med. 2007; 33(6 Suppl):S406–13.

192. Hawkins J, Hollingworth W, Campbell R. Long-term smoking relapse: a study using the British household panel survey. Nicotine Tob Res. 2010; 12(12):1228–35.

193. Prochaska JJ. Failure to treat tobacco use in mental health and addiction treatment settings: a form of harm reduction? Drug Alcohol Depend. 2010; 110(3):177–82.

194. Varsano S, Ganz I, Eldor N, Garenkin M. Water-pipe tobacco smoking among school children in Israel: frequencies, habits, and attitudes. Harefuah. 2003; 142(11):736–41,807.

195. Grimshaw GM, Stanton A. Tobacco cessation interventions for young people. Cochrane Database Syst Rev. 2006; 4:CD003289. Available from: http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD003289/pdf_fs.html (accessed December 2011).

196. Curry SJ, Mermelstein RJ, Sporer AK. Therapy for specific problems: youth tobacco cessation. Annu Rev Psychol. 2009; 60:229–55. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2811429 (accessed December 2011).

197. Sussman S, Sun P, Dent CW. A meta-analysis of teen cigarette smoking cessation. Health Psychol. 2006; 25(5):549–57.

198. Turan A, Mascha EJ, Roberman D, *et al*. Smoking and perioperative outcomes. Anesthesiology. 2011; 114(4):837–46.

199. Edmonston DL, Foulkes GD. Infection rate and risk factor analysis in an orthopaedic ambulatory surgical center. J Surg Orthop Adv. 2010; 19(3):174–6.

200. Mills E, Eyawo O, Lockhart I, Kelly S, Wu P, Ebbert JO. Smoking cessation reduces postoperative complications: a systematic review and meta-analysis. Am J Med. 2011; 124(2):144–54.

201. Rigotti NA, Munafo MR, Stead LF. Interventions for smoking cessation in hospitalised patients. Cochrane Database Syst Rev. 2007 Jul 18; 3:CD001837. Available from: http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD001837/frame.html (accessed December 2011).

202. Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: varenicline. Int J Clin Pract. 2006; 60(5):571–6.

203. Quaak M, van Schayck CP, Knaapen AM, van Schooten FJ. Genetic variation as a predictor of smoking cessation success. A promising preventive and intervention tool for chronic respiratory diseases? Eur Respir J. 2009; 33(3):468–80. Available from: http://erj.ersjournals.com/content/33/3/468.long (accessed December 2011).

204. Cinciripini PM, Hecht SS, Henningfield JE, Manley MW, Kramer BS. Tobacco addiction: implications for treatment and cancer prevention. J Natl Cancer Inst. 1997; 89(24):1852–67. Available from: http://jnci.oxfordjournals.org/content/89/24/1852.full (accessed December 2011).

205. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2008; 1:CD000146. Available from: http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD000146/frame.html (accessed December 2011).

206. Kishore SP, Bitton A, Cravioto A, Yach D. Enabling access to new WHO essential medicines: the case for nicotine replacement therapies. Global Health. 2010; 6:22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2994846 (accessed December 2011).

207. Zapawa LM, Hughes JR, Benowitz NL, Rigotti NA, Shiffman S. Cautions and warnings on the US OTC label for nicotine replacement: what's a doctor to do? Addict Behav. 2011; 36(4):327–32.

208. Ford CL, Zlabek JA. Nicotine replacement therapy and cardiovascular disease. Mayo Clin Proc. 2005; 80(5):652–6. Available from: http://www.mayoclinicproceedings.com/content/80/5/652.long (accessed December 2011).

209. Reid RD, Pipe AL, Quinlan B. Promoting smoking cessation during hospitalization for coronary artery disease. Can J Cardiol. 2006; 22(9):775–80. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2560518/ (accessed December 2011).

210. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. J Am Coll Cardiol. 1997; 29(7):1422–31.

211. Boots Company PLC. Boots NicAssist 10 mg Patch, Summary of Product Characteristics. April 2010. Available from: http://www.medicines.org.uk/EMC/medicine/23303/SPC/Boots+NicAssist+10+mg+Patch/ (accessed December 2011).

212. Benowitz N, Dempsey D. Pharmacotherapy for smoking cessation during pregnancy. Nicotine Tob Res. 2004; 6(Suppl 2):S189–202.

213. Osadchy A, Kazmin A, Koren G. Nicotine replacement therapy during pregnancy: recommended or not recommended? J Obstet Gynaecol Can. 2009; 31(8):744–7.

214. Forinash AB, Pitlick JM, Clark K, Alstat V. Nicotine replacement therapy effect on pregnancy outcomes. Ann Pharmacother. 2010; 44(11):1817–21.

215. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. Pediatrics. 2001; 108(3):776–89. Available from: http://pediatrics.aappublications.org/cgi/reprint/108/3/776 (accessed December 2011).

216. Rosen IM, Maurer DM. Reducing tobacco use in adolescents. Am Fam Physician. 2008; 77(4):483–90. Available from: http://www.aafp.org/afp/2008/0215/p483.html (accessed December 2011).

217. Tønnesen P, Paoletti P, Gustavsson G, *et al*. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. Collaborative European Anti-Smoking Evaluation. European Respiratory Society. Eur Respir J. 1999; 13(2):238–46.

218. Shiffman S, Khayrallah M, Nowak R. Efficacy of the nicotine patch for relief of craving and withdrawal 7–10 weeks after cessation. Nicotine Tob Res. 2000; 2(4):371–8.

219. Henningfield JE, Fant RV, Buchhalter AR, Stitzer ML. Pharmacotherapy for nicotine dependence. CA Cancer J Clin. 2005; 55(5):281–99. Available from: http://caonline.amcancersoc.org/cgi/content/full/55/5/281 (accessed December 2011).

220. Molander L, Lunell E. Pharmacokinetic investigation of a nicotine sublingual tablet. Eur J Clin Pharmacol 2001; 56:813–9.

221. McNeil Products Ltd. Nicorette Microtab Lemon 2 mg sublingual tablets, Summary of Product Characteristics. August 2009. Available from: http://www.medicines.org.uk/EMC/medicine/22215/SPC/Nicorette+Microtab+Lemon+2+mg+sublingual+tablets./ (accessed December 2011).

222. Bolliger CT, van Biljon X, Axelsson A. A nicotine mouth spray for smoking cessation: a pilot study of preference, safety and efficacy. Respiration. 2007; 74(2):196–201.

223. McNeil Products Ltd. Nicorette QuickMist 1mg/spray mouthspray, Summary of Product Characteristics. February 2011. Available from: http://www.medicines.org.uk/EMC/medicine/24257/SPC/Nicorette+QuickMist+1mg+spray+mouthspray/ (accessed December 2011).

224. Bolliger CT, Zellweger JP, Danielsson T, *et al*. Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. BMJ. 2000; 321(7257):329–33. Available from: http://www.bmj.com/content/321/7257/329.long (accessed December 2011).

225. Bolliger CT, Zellweger JP, Danielsson T, *et al*. Influence of long-term smoking reduction on health risk markers and quality of life. Nicotine Tob Res. 2002; 4(4):433–9.

226. Fagerström KO, Hughes JR. Nicotine concentrations with concurrent use of cigarettes and nicotine replacement: a review. Nicotine Tob Res. 2002; 4(Suppl 2):S73–9.

227. Schuurmans MM, Diacon AH, van Biljon X, Bolliger CT. Effect of pre-treatment with nicotine patch on withdrawal symptoms and abstinence rates in smokers subsequently quitting with the nicotine patch: a randomized controlled trial. Addiction. 2004; 99(5):634–40.

228. Rose JE, Herskovic JE, Behm FM, Westman EC. Precessation treatment with nicotine patch significantly increases abstinence rates relative to conventional treatment. Nicotine Tob Res. 2009; 11(9):1067–75.

229. Scharf D, Shiffman S. Are there gender differences in smoking cessation, with and without bupropion? Pooled- and meta-analyses of clinical trials of Bupropion SR. Addiction. 2004; 99:1462–9.

230. Richmond R, Zwar N. Review of bupropion for smoking cessation. Drug Alcohol Rev. 2003; 22(2):203–20.

231. Evins AE, Culhane MA, Alpert JE, *et al*. A controlled trial of bupropion added to nicotine patch and behavioral therapy for smoking cessation in adults with unipolar depressive disorders. J Clin Psychopharmacol. 2008; 28(6):660–6.

232. GlaxoSmithKline. Zyban (bupropion hydrochloride) Sustained-Release Tablets, Prescribing Information. Updated September 2010. Available from: http://us.gsk.com/products/assets/us_zyban.pdf (accessed December 2011).

233. Tschabitscher P, Homaier I, Lichtenschopf A, Groman E. Varenicline - pharmacological therapy of tobacco dependence. Expert Opin Pharmacother. 2007; 8(11):1757–67.

234. Faessel HM, Obach RS, Rollema H, Ravva P, Williams KE, Burstein AH. A review of the clinical pharmacokinetics and pharmacodynamics of varenicline for smoking cessation. Clin Pharmacokinet. 2010; 49(12):799–816.

235. Garrison GD, Dugan SE. Varenicline: a first-line treatment option for smoking cessation. Clin Ther. 2009; 31(3):463–91.

236. Gonzales D, Rennard SI, Nides M, *et al*. Varenicline, an alpha 4 beta 2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006; 296(1):47–55. Available from: http://jama.ama-assn.org/content/296/1/47.long (accessed December 2011).

237. Jorenby DE, Hays JT, Rigotti NA, *et al*. Efficacy of varenicline, an alpha 4 beta 2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006; 296(1):56–63.

238. 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.

239. 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.

240. Bolliger CT, Issa JS, Posadas-Valay R, *et al*. A randomized trial of varenicline for smoking cessation in Latin America, Africa and the Middle East. Clin Ther. 2011; 33(4):465–77.

241. Pfizer. CHANTIX®(varenicline) Tablets. Highlights of prescribing information. Updated July 2011. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=557 (accessed December 2011).

242. Hajek P, Tønnesen P, Arteaga C, Russ C, Tonstad S. Varenicline in prevention of relapse to smoking: effect of quit pattern on response to extended treatment. Addiction. 2009; 104(9):1597–602.

243. Tonstad S, Tønnesen P, Hajek P, *et al*. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA. 2006; 296(1):64–71.

244. 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. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2962400 (accessed December 2011).

245. Tonstad S, Davies S, Flammer M, Russ C, Hughes J. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. Drug Saf. 2010; 33(4):289–301.

246. 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. Available from: http://www.cmaj.ca/content/183/12/1359.long (accessed December 2011).

247. Hays JT. Varenicline for smoking cessation: is it a heartbreaker? (Editorial). CMAJ. 2011; 183(12):1346–7.

248. Samuels L. Varenicline: cardiovascular safety. (Letter). CMAJ. 2011; 183(12):1407–8. Available from: http://www.cmaj.ca/content/183/12/1407 (Accessed December 2011).

249. European Medicine Agency. European Medicines Agency confirms positive benefit–risk balance for Champix. Benefits as a smoking cessation medicine outweigh slight reported increase in cardiovascular events. Available from: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/07/news_detail_001314.jsp&mid=WC0b01ac058004d5c1&murl=menus/news_and_events/news_and_events.jsp&jsenabled=true (accessed December 2011).

250. da Costa CL, Younes RN, Lourenço MT. Stopping smoking: a prospective, randomized, double-blind study comparing nortriptyline to placebo. Chest. 2002; 122(2):403–8.

251. Hughes JR, Stead LF, Lancaster T. Nortriptyline for smoking cessation: a review. Nicotine Tob Res. 2005; 7(4):491–9.

252. Prochazka AV, Kick S, Steinbrunn C, Miyoshi T, Fryer GE. A randomized trial of nortriptyline combined with transdermal nicotine for smoking cessation. Arch Intern Med. 2004; 164(20):2229–33.

253. Aveyard P, Johnson C, Fillingham S, Parsons A, Murphy M. Nortriptyline plus nicotine replacement versus placebo plus nicotine replacement for smoking cessation: pragmatic randomised controlled trial. BMJ. 2008; 336(7655):1223–7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2405820/ (accessed December 2011).

254. Gourlay SG, Stead LF, Benowitz NL. Clonidine for smoking cessation. Cochrane Database Syst Rev. 2000; 2:CD000058. Available from: http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/rel0001/CD000058/pdf_fs.html (accessed December 2011).

255. Ebbert JO, Burke MV, Hays JT, Hurt RD. Combination treatment with varenicline and nicotine replacement therapy. Nicotine Tob Res. 2009; 11(5):572–6.

256. Ebbert JO, Croghan IT, Sood A, Schroeder DR, Hays JT, Hurt RD. Varenicline and bupropion sustained-release combination therapy for smoking cessation. Nicotine Tob Res. 2009; 11(3):234–9.

257. Ebbert JO, Hays JT, Hurt RD. Combination pharmacotherapy for stopping smoking: what advantages does it offer? Drugs. 2010; 70(6):643–50.

Appendix

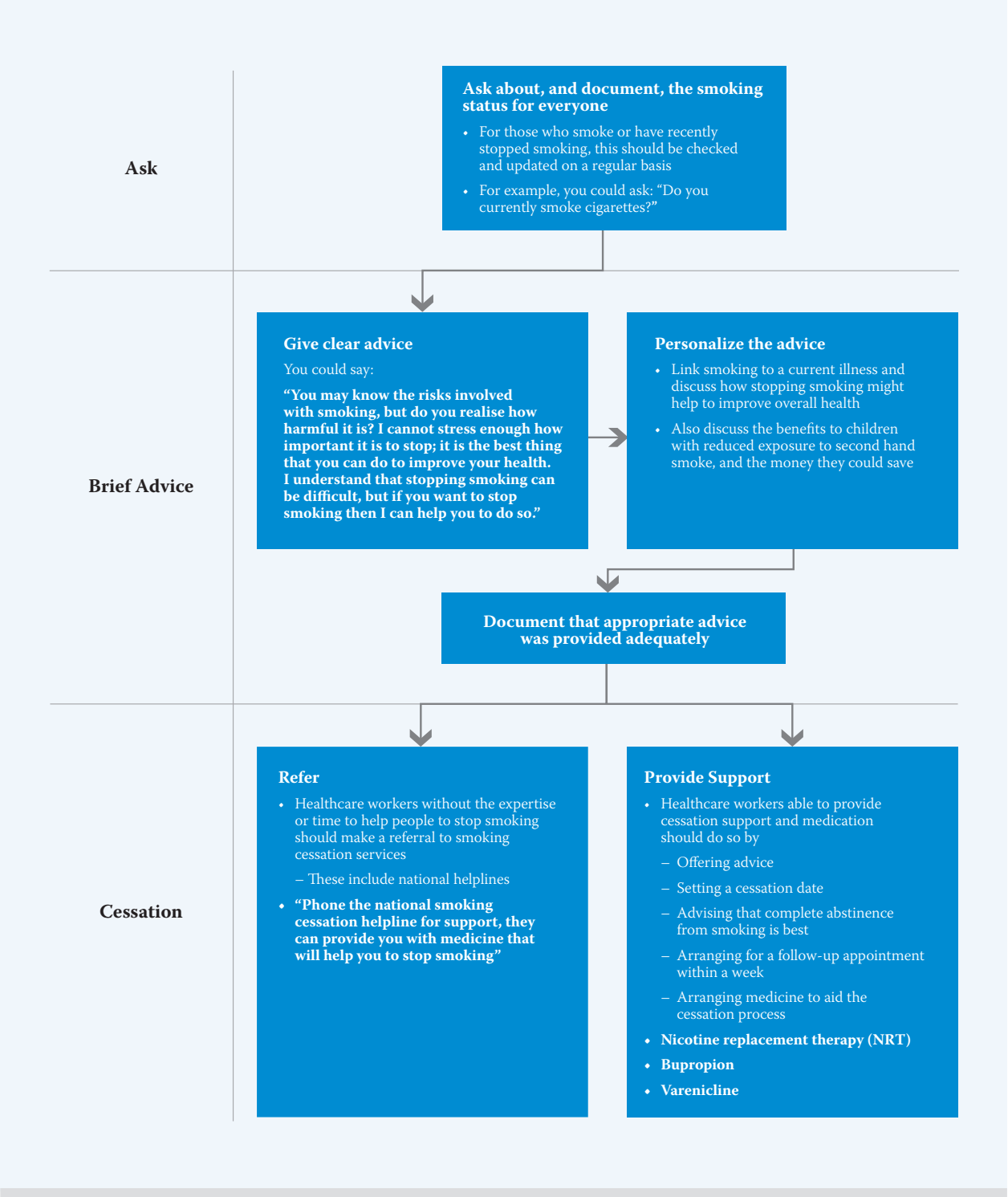

Figure 9: The ABC algorithm for smoking cessation[135]