III. FAMILY MEDICINE FOR MEDICAL STUDENTS

Introduction to Family Medicine / General Practice
László Kalabay MD, PhD

Levels of health care

Primary care physician: A physician from whatever discipline working in a primary care setting.

Secondary care physician: A physician who has undergone a period of higher postgraduate training in an organ/disease based discipline, and who works predominantly in that discipline in a hospital setting.

Specialist: A physician from whatever discipline who has undergone a higher postgraduate training.

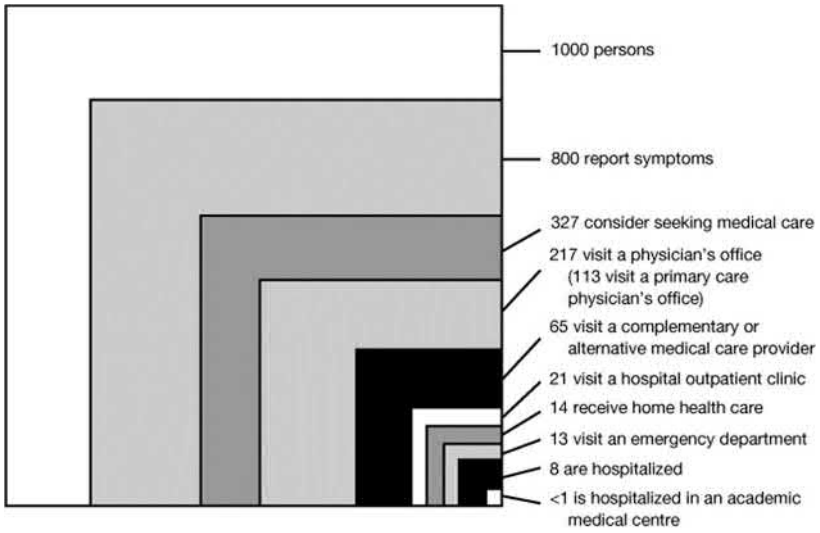

Figure 1. The ecology of medical care revisited (Green, 2001) [1]). As a consequence of data depicted shows the bulk (90% in Hungary) of the doctor-patient encounters take place in the primary care setting. The family physician has a gatekeeper function. In addition, prevention can be performed only in the primary care setting.

Basic definitions in general medicine

General Practitioner / Family Doctor: Synonyms, used to describe those doctors who have undergone postgraduate training in general practice at least to the level defined in Title 4 of the Doctors' Directive.

General Practice / Family Medicine: An academic and scientific discipline, with its own educational content, research, evidence base and clinical activity, and a clinical specialty oriented to primary care.

What is primary care good for?

- Barbara Starfield (Report)
- Each additional general practitioner per 10,000 population (a 15-20% increase) is associated with a decrease in mortality of about 6% (Gulliford 2002).
- The ratio of general practitioners to population was significantly associated with lower all-cause mortality, acute myocardial infarction mortality, avoidable mortality, hospital admissions (both chronic and acute), and teenage pregnancies (Gulliford 2004).

- The structural characteristics of primary care practices may have more of an impact on health outcomes than the mere presence of primary care physicians.

Models of primary care all throughout the world

Name of the model	The role of the health visitor
Extended general practice	Specialist nurse responsible for occupational health, prevention and environmental / community development - population wide.
Managed care enterprise	A sessional worker targeting high score DALYS index patients with high referral / readmission rates and administering cost-effective screening programs.
Reformed polyclinic	A clinical specialist site-based receiving direct patient referrals in relation to clinic / commissioning prescribed protocols and programs for Fee for Service (e.g. inoculations).
District health system	Frontline health station practitioner combining health promotion with acute and primary care under remote supervision of district public health / medical officer, with important local support from charities and churches.
Community development agency	Expenses only health care technician undertaking 6 monthly Household Health Assessment visits with targeted 'Health Impact' follow ups by local family doctor and nurse. Leader of 5 person health promoter volunteer team each responsible for one local health priority.
"Franchised Outreach"	Outside health service employed on municipal public health campaigns and accountable to elected councilors. Part of social welfare services.

(Courtesy of dr. Geoffrey Meads, 2009)

The history family medicine

- General Practitioner, Family Doctor, Medicus Universalis
- Should there be a doctor, who is readily available, knows and is responsible for everything
- In addition is a close friend
- The image of the „benevolent good old doctor"

The birth of family practice

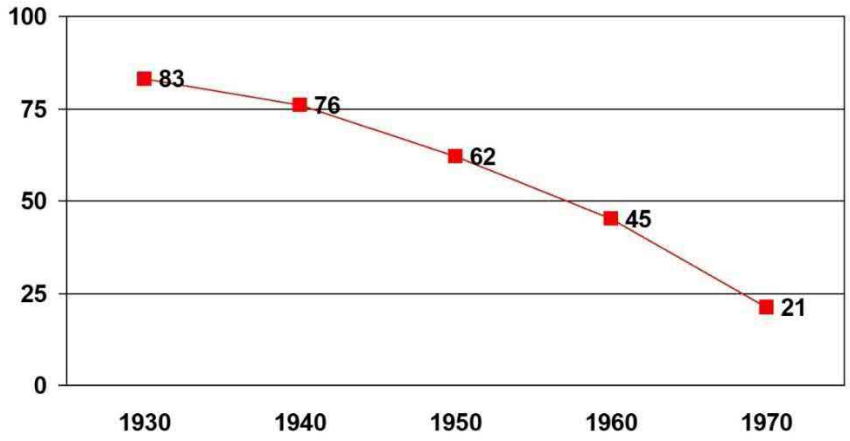

Figure 2. Per cent of American physicians in practice as GP, 1930-1970. [2] The continuously declining percentage of family doctors threatened the public health. This situation called for family medicine as a separate discipline.

- 1930: Francis Peabody: fragmentation, specification ↔ GP's approach
- 1966: Family practice as a unique discipline in the USA
- 1969: American Board of Family Practice
- 1975: Board of Family Medicine in Hungary

General Practice – An Initial Approach

- Essential part of medical care in all countries.
- The GP is the first point of contact for most medical services.
- Wide range of consultations and home visits.
- GPs provide a complete spectrum of care within the local community – education, prevention, treatment.
- No other specialty offers such a wide remit of treating everything from babies and from mental illnesses to sports medicine.
- The opportunity of prevention is given only at the level of the GP.
- Most GPs are independent contractors of the national health system.

The reform of national health systems

- Changes in: demography; medical advances; health economics; patient needs and expectations
- International evidences indicate: health systems based on effective primary care with highly trained generalist physicians provide both more cost and clinically effective care
- Ever increasing importance of FM/GP

The definition of family practice: WHO, EURACT, WONCA/Europe (2002)

- Differences in the way of FM/GP organised and provided in Europe
- Medical education is governed by EU Directive 93/16 - free movement of doctors
- Training should equip with skills necessary to practice in any member state
- WONCA Europe definition of the discipline; professional tasks; core competencies

The Three Components of the European Definition

I. A description of the characteristics of the discipline

II. Description of the role of the GP

III. List of core competencies (6), implementation areas (3) and fundamental features

I. The characteristics of the discipline

1. Is normally the point of first medical contact within the health care system, providing open and unlimited access to its users, dealing with all health problems regardless of age, sex, or any other characteristic of the person concerned.
2. Makes efficient use of health care resources through co-ordinating care, working with other professionals in the primary care setting, and by managing the interface with other specialties taking an advocacy role for the patients when needed.
3. Develops a person-centred approach, oriented to the individual, his/her family, and their community.
4. Has a unique consultation process, which establishes a relationship over time, through the effective communication between doctor and patient.
5. Is responsible for the provision of longitudinal continuity of care as determined by the needs of the patient.

6. Has a specific decision-making process determined by the prevalence and incidence of illness in the community.
7. Manages simultaneously both acute and chronic health problems of individual patients.
8. Manages illness which presents in an undifferentiated way at an early stage in its development, which may require urgent intervention.
9. Promotes health and wellbeing both by appropriate and effective intervention.
10. Has a specific responsibility for the health of the community.
11. Deals with health problems in their physical, social, cultural and existential dimensions.

II. The Specialty of General Practice / Family Medicine

General practitioners:

- Are specialist physicians trained in the principles of the discipline.
- Are personal doctors, primarily responsible for the provision of comprehensive and continuing care to every individual seeking medical care irrespective of age, sex and illness.
- Care for individuals in the context of their family, their community and their culture, always respecting the autonomy of their patients.
- Recognized they also have a professional responsibility to their community.
- In negotiating management plans with their patients they integrate physical, psychological, social, cultural, and existential factors, utilising the knowledge and trust engendered by repeated contacts.
- Exercise their professional role by promoting health, preventing disease and providing cure, care or palliation.
- This is done either directly or through the services of others according to their health needs and resources available within the community they serve, assisting patients where necessary in accessing these services.
- Must take the responsibility for developing and maintaining their skills, personal balance and values as a basis for effective and safe patient care.

III. The Core Competencies of the GP/FM

12. Primary care management
13. Person-centred care
14. Specific problem solving skills
15. Comprehensive approach
16. Community orientation
17. Holistic modelling

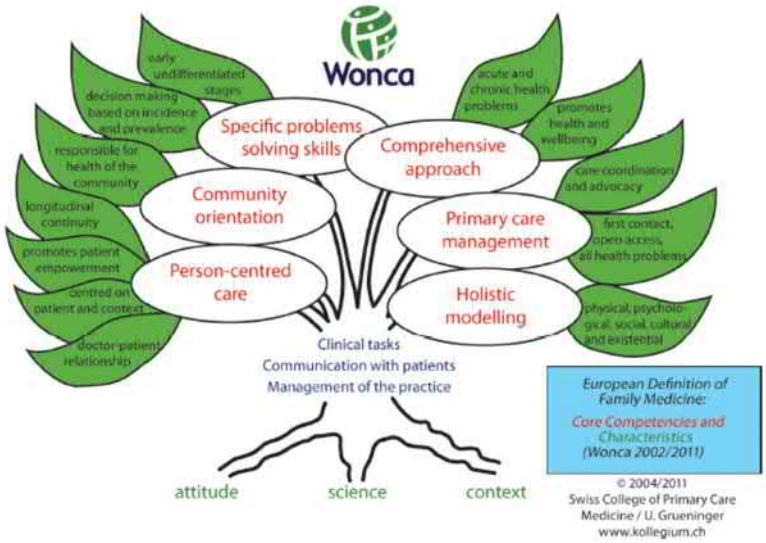

Figure 3. The main characteristics of family medicine. The WONCA Tree (Courtesy of U. Grueninger, Swiss College of Primary Care, 2011)

III/1. Primary Care Management Abilities

- to manage primary contact with patients, dealing with unselected problems
- to cover the full range of health conditions
- to co-ordinate care with other professionals
- to master effective and appropriate care provision and health service utilisation
- to make available to the patient the appropriate services within the health care system
- to act as advocate for the patient

III/2. Abilities of Providing Person-Centred Care

- to adopt a person-centred approach in dealing with patients and problems in the context of
- patient's circumstances
- to apply the GP consultation to bring about an effective doctor-patient relationship with respect for the patient's autonomy
- to communicate, set priorities and act in partnership
- to provide longitudinal continuity of care as determined by the needs of the patient, referring to continuing and co-ordinated care management

III/3. Specific Problem-Solving Skills

- to relate specific decision making processes to the prevalence and incidence of illness in the community
- to selectively gather and interpret information from history taking, physical examination, and investigations and apply it to an appropriate management plan in collaboration with the patient
- to adopt appropriate working principles e.g. incremental investigation, using time as a tool, and to tolerate uncertainty

- to intervene urgently when necessary
- to manage conditions which may present early and undifferentiated way
- to make effective and efficient use of diagnostic and therapeutic interventions

III/4. Comprehensive Approach Abilities

- to manage simultaneously multiple complaints and pathologies, both acute and chronic health problems in the individual
- to promote health and wellbeing by applying health promotion and disease prevention strategies appropriately
- to manage and co-ordinate health promotion, prevention, cure, care and palliation and rehabilitation

III/5. Community Orientation Abilities

- Community orientation includes the ability to reconcile the health needs of individual patients and the health needs of the community in which they live in balance with available resources

III/6. Holistic Modelling Abilities

- Holistic modelling includes the ability to use a bio-psycho-social model taking into account cultural and existential dimensions. To practice the speciality, the competent practitioner implements these competencies in three important areas:

a) Clinical tasks

b) Communication with patients and

c) Management of practice

As a person-centred scientific discipline, three background features should be considered as fundamental:

a) Contextual: using the context of the person, the family, the community and their culture

b) Attitudinal: based on the doctor's professional capabilities, values and ethics

c) Scientific: adopting a critical and research based on approach to practice and maintaining this through continuing learning and quality improvement.

GMC for GPs - Good Clinical Care

The unacceptable GP:

- Has limited competence, and is unaware of where his or her competence lies
- Consistently ignores, interrupts or contradicts his or her patients
- Fails to elicit important parts of the history
- Is unable to discuss sensitive and personal matters with patients
- Fails to use the medical records as a source of information about past events
- Fails to examine patients when needed
- Undertakes inappropriate, cursory, or inadequate examinations
- Does not possess or fails to use appropriate diagnostic and treatment equipment
- Consistently undertakes inappropriate investigations

- Show little evidence of a coherent or rational approach to diagnosis
- Draws illogical conclusions from the information available
- Gives treatments that are inconsistent with best practice or evidence
- Has no way of organising care for long-term problems or for prevention
- Keeps records which are incomplete or illegible, and contain inaccurate details or gratuitously derogatory remarks
- Does not keep records confidential
- Does not take account of colleagues' legitimate need for information
- Keeps records that cannot readily be followed by another doctor
- Consistently consults without records
- Omits important information from a report which he or she has agreed to provide, or includes untruthful information in such a report.
- Has very restricted opening hours
- Does not have adequate arrangements for patients to contact the practice by phone
- Provides no opportunity for patients to talk to a doctor or a nurse on the phone
- Cannot be contacted when on duty, takes a long time to respond to calls, or does not take rapid action in an emergency situation
- Has no system for transferring information about out-of-hours consultations to the patient's usual doctor
- Does not follow up relevant information about his or her patients that has been provided by another health professional.
- Ignores the patient's best interests when deciding about treatment or referral
- Consistently ignores, interrupts, or contradicts his or her patients
- Is careless of the patient's dignity, and assumes his or her willingness to submit to examination without seeking permission
- Makes little effort to ensure that patient has understood his or her condition, its treatment, and prognosis
- Is careless with confidential information
- Fails to obtain patients' consent to treatment
- Has inappropriate financial or personal relationships with patients
- Provides better care to some patients than others as a result of his or her own prejudice
- Pressurises patients to act in line with his or her own beliefs and values
- Refuses to register certain categories of patients, such as the homeless, the severely mentally ill, or those with problems or substance or alcohol misuse
- Does not attempt to meet members of the primary care team (e.g. district nurses, health visitors), or even know who they are
- Does not know how to contact primary care team members
- Does not know what skills team members have
- Delegates tasks to other members of the team for which they do not have appropriate skills
- Does not encourage staff to develop new skills and responsibilities
- Does not refer patients when specialist care is necessary
- Consistently dismisses patients' request for a second opinion
- Consistently refers patients for care which would normally be regarded as part of general practice
- Does not provide information in a referral that enables the specialist to give appropriate care

WH Auden: Give me a doctor …	Marie Campkin: Give me a doctor … (?)
Give me a doctor, partridge plump *Short in the leg and broad in the rump* *An endomorph with gentle hands* *Who'll never make absurd demands* *That I abandon all my vices,* *Nor pull a long face in a crisis,* *But with a twinkle in his eye* Will tell me that I have to die.	*Give me a doctor, underweight,* *Computerised and up-to-date,* *A businessman who understands* *Accountancy and target bands,* *Who demonstrates sincere devotion* *To audit and health promotion -* *But when my outlook's for the worse* Refers me to the Practice Nurse.

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Cardiovascular Diseases in Family Medicine

János Nemcsik MD, PhD

Clinical Manifestations of cardiovascular (CV) diseases

Coronary heart disease	Cerebrovascular disease	Peripheral artery disease
• angina pectoris • myocardial infarction • sudden cardiac death	• transient ischemic attack (TIA) • stroke	• intermittent claudication • gangrene

Why is prevention of CV diseases needed?

- Atherosclerotic CVD, especially CHD, remains the leading cause of premature death worldwide.
- CVD affects both men and women; of all deaths that occur before the age of 75 years in Europe, 42% are due to CVD in women and 38% in men.
- CVD mortality is changing, with declining age-standardized rates in most European countries, which remain high in Eastern Europe.
- Prevention works: 50% of the reductions seen in CHD mortality is related to changes in risk factors, and 40% to improved treatments.

Mortality: Cardiovascular diseases and diabetes, deaths per 100,000 (http://apps.who.int/gho/data/?vid=2510)

	Male	Female
Hungary	416	241
USA	190	122
Spain	140	86
France	128	69
Russia	772	414
Mali	419	393

Risk factors for cardiovascular disease

Modifiable	Non-modifiable
• Smoking • Dyslipidaemia (raised LDL-C, low HDL-C, raised triglycerides) • Raised blood pressure • Diabetes mellitus • Obesity • Dietary factors • Thrombogenic factors • Lack of exercise • Excess alcohol consumption	• Personal history of CHD • Family history of CHD • Age • Gender

Different appearances of atherosclerosis

- Transient ischemic attack
- Ischemic stroke
- Heart attack
- Angina (stable, instable)
- Renovascular hypertension
- Renal insufficiency
- Peripheral artery disease

Figure 1. The cardiovascular system. Adapted from [1].

Prevention-definitions

- Primary prevention strategies intend to avoid the development of disease.
- Secondary prevention strategies attempt to diagnose and treat an existing disease in its early stages before it results in significant morbidity.
- Tertiary prevention: these treatments aim to reduce the negative impact of established disease by restoring function and reducing disease-related complications.

Recent cardiovascular prevention guideline [2]:

"The physician in general practice is the key person to initiate, coordinate and provide long-term follow-up for CVD prevention. In most countries, GPs deliver 90% of consultations and provide most public health medicine, including preventive care and chronic disease monitoring. In the case of CVD prevention, they have a unique role in identifying individuals at risk of CVD and assessing their eligibility for intervention based on their risk profile."

How to stay healthy?

- No use of tobacco
- Adequate physical activity: at least 30 min five times a week

- Healthy eating habits
- No overweight
- Blood pressure below 140/90 mmHg
- Blood cholesterol below 5 mmol/L (190 mg/dL)
- Normal glucose metabolism
- Avoidance of excessive stress

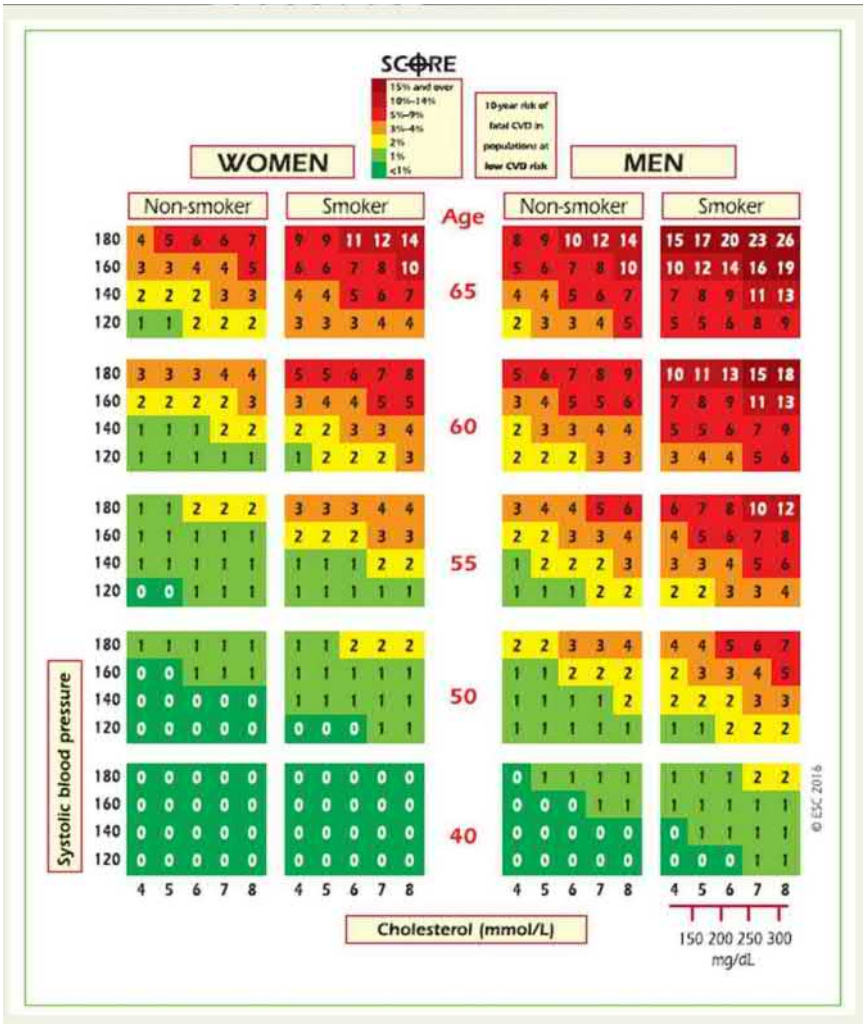


Figure 2. 10-year risk of fatal CVD in low risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status. Adapted from [2].

Calculate score at: www.hearscore.org

Risk stratification: very high CV risk

- Coronary artery disease, cerebrovascular disease or peripheral artery disease
- Diabetes mellitus: type 1 /2 with one or more CV risk factors and/or target organ damage (micro/macroalbuminuria)
- Chronic renal insufficiency (GFR<30 ml/min/1.73 m^2)
- 10-year mortality ≥10%

Risk stratification: high CV risk

Free of CV symptoms, high risk groups:

- At least one severe risk factor is present:
- total cholesterol >8.0 mmol/l
- blood pressure >180/110 mmHg
- DM without target organ damage
- glomerular filtration rate 30-59 ml/min/1.73 m^2
- score of ≥ 5% and < 10% of 10-year risk of fatal CVD

At least one, severe risk factor:

- Subclinical atherosclerosis: presence of a calcified plaque
- Familiarity- early CV episode: < 55 /< 65 year
- Left ventricular hypertrophy
- Metabolic syndrome

Global risk factors:

- ≥ 3 traditional cardiometabolic risk factors (smoking, abdominal obesity, hypertension, hypercholesterinemia and/or high LDL, low HDL) and
- ≥ 1 „residual" risk factor (IFG/IGT, elevated Tg, elevated uric acid, sleep apnoe) is present, even if the total risk score is <5%

Psychosocial risk factors

Contribute both to the risk of developing CVD and the worsening of clinical course and prognosis of CVD:

- low socio-economic status
- lack of social support
- stress at work and in family life
- depression, anxiety, hostility
- type D personality

• Spend enough time with the individual to create a therapeutic relationship—even a few more minutes can make a difference.
• Acknowledge the individual's personal view of his/her disease and contributing factors.
• Encourage expression of worries and anxieties, concerns, and self-evaluation of motivation for behaviour change and chances of success.
• Speak to the individual in his/her own language and be supportive of every improvement in lifestyle.
• Ask questions to check that the individual has understood the advice and has any support they require to follow it.
• Acknowledge that changing life-long habits can be difficult and that gradual change that is sustained is often more permanent than a rapid change.
• Accept that individuals may need support for a long time and that repeated efforts to encourage and maintain lifestyle change may be necessary in many individuals.
• Make sure that all health professionals involved provide consistent information.

Figure 3. Principles of effective communication to facilitate behavioural change. Adapted from [3].

Hypertension management

Based on the recent European guideline [4].

Category	SBP		DBP
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

The blood pressure (BP) category is defined by the highest BP level, whether systolic blood pressure (SBP) or diastolic blood pressure (DBP). Isolated systolic hypertension should be graded 1, 2 or 3 according to SBP values in the ranges indicated.

Figure 4. Blood pressure categories

How to measure the blood pressure?

- Allow the patient to sit for 3-5 minutes before beginning BP measurement.

- Take at least two BP measurements spaced 1-2 min apart, and additional measurements if the first two are quite different.
- Repeated measurements in atrial fibrillation.
- Use standard bladder (12-13 cm), but have larger and smaller as well for large and thin arms.
- Measure at first visit BP 1 and 3 min after assumption of the standing position in elderly participants, diabetic patients and in other conditions in which orthostatic hypertension may be frequent or suspected.

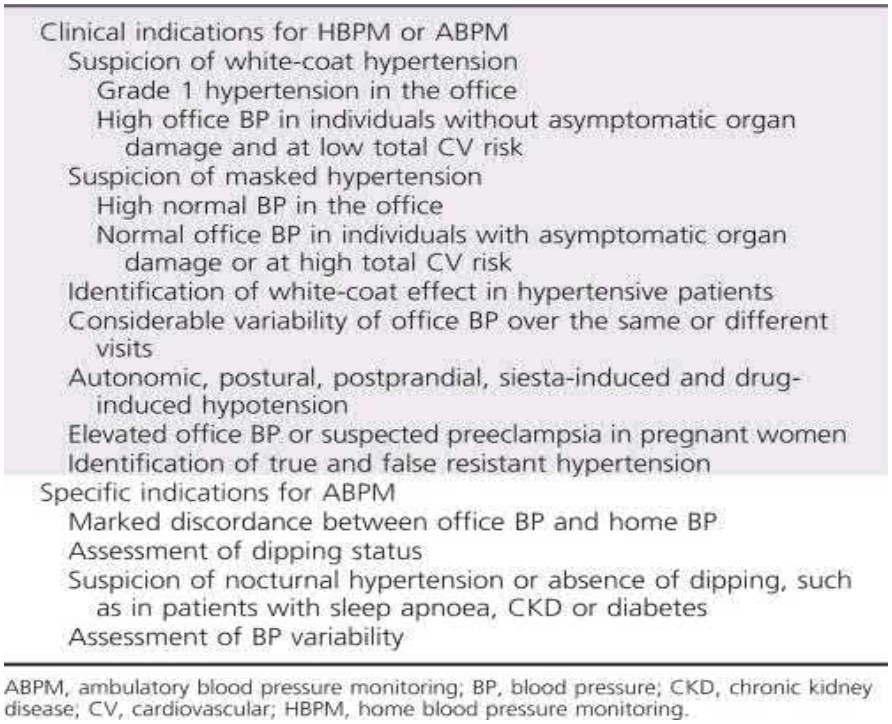


Figure 5. Clinical indications of home blood pressure monitoring (HBPM) or ambulatory blood pressure monitoring (ABPM)

Table 3 **Classification of office blood pressure[a] and definitions of hypertension grade[b]**

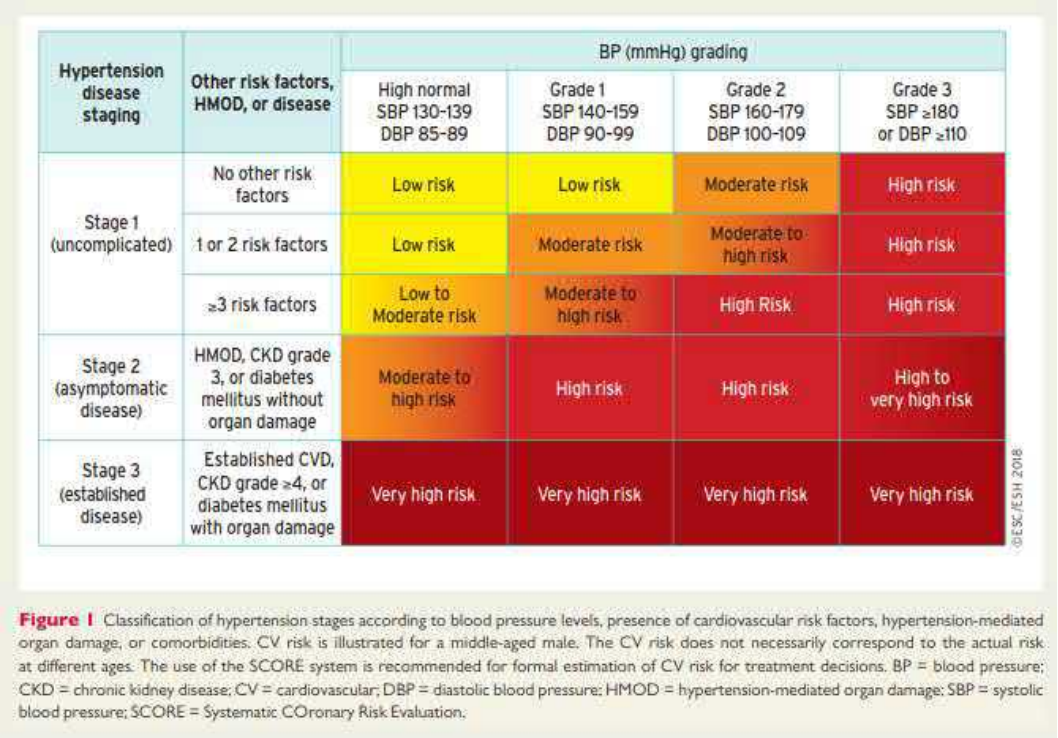
Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

BP = blood pressure; SBP = systolic blood pressure.
[a]BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.
[b]Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.
The same classification is used for all ages from 16 years.

Figure 6. Normal ranges of blood pressure

Signs suggesting secondary hypertension

- features of Cushing syndrome
- skin stigmata of neurofibromatosis (pheochromocytoma)
- palpation of enlarged kidneys (polycystic kidney)
- auscultation of abdominal murmurs (renovascular hypertension)
- auscultation of precordial chest murmurs (aortic coarctation, aortic disease: upper extremity artery disease)
- left-right arm blood pressure difference (aortic coarctation, subclavian artery stenosis)



Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥3 risk factors	Low to Moderate risk	Moderate to high risk	High Risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

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Figure 1 Classification of hypertension stages according to blood pressure levels, presence of cardiovascular risk factors, hypertension-mediated organ damage, or comorbidities. CV risk is illustrated for a middle-aged male. The CV risk does not necessarily correspond to the actual risk at different ages. The use of the SCORE system is recommended for formal estimation of CV risk for treatment decisions. BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure; SCORE = Systematic COronary Risk Evaluation.

Figure 7. Cardiovascular risk and blood pressure

Risk factors

- Male sex
- Age (men ≥55 years; women ≥65 years)
- Smoking
- Dyslipidaemia
- Total cholesterol >4.9 mmol/L (190 mg/dL), and/or
- Low-density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL), and/or high-density lipoprotein cholesterol: men <1.0 mmol/L (40 mg/dL), women <1.2 mmol/L (46 mg/dL), and/or triglycerides >1.7 mmol/L (150 mg/dL)
- Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)
- Abnormal glucose tolerance test
- Obesity (BMI ≥30 kg/m^2)
- Abdominal obesity (waist circumference: men ≥102 cm; women ≥88 cm) (in Caucasians)
- Family history of premature CVD (men aged <55 years; women aged <65 years)

Asymptomatic organ damage

- Pulse pressure (in the elderly) ≥60 mmHg
- Electrocardiographic LVH (Sokolow–Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV*ms), or Echocardiographic LVH [LVM index: men >115 g/m2; women >95 g/m2 (BSA)]
- Carotid wall thickening (IMT >0.9 mm) or plaque
- Carotid–femoral PWV >10 m/s
- Ankle-brachial index <0.9
- Microalbuminuria (30–300 mg/24 h), or albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine)

Diabetes mellitus

- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) on two repeated measurements, and/or
- HbA1c >7% (53 mmol/mol), and/or post-load plasma glucose >11.0 mmol/L (198 mg/dL)

Established CV or renal disease

- Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack
- CHD: myocardial infarction; angina; myocardial revascularization with PCI or CABG
- Heart failure, including heart failure with preserved EF
- Symptomatic lower extremities peripheral artery disease
- CKD with eGFR <30 mL/min/1.73m2; proteinuria (>300 mg/24 h)
- Advanced retinopathy: haemorrhages or exudates, papilloedema

Routine tests
Haemoglobin and/or haematocrit
Fasting plasma glucose
Serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol
Fasting serum triglycerides
Serum potassium and sodium
Serum uric acid
Serum creatinine (with estimation of GFR),
Urine analysis: microscopic examination; urinary protein by dipstick test; test for microalbuminurea
12-lead EGG.
Additional tests, based on history, physical examination and findings from routine laboratory tests
Haemoglobin A_{1c} [if fasting plasma glucose is >5.6 mmol/l (102 mg/dl) or previous diagnosis of diabetes]
Quantitative proteinuria (if dipstick test is positive); urinary potassium and sodium concentration and their ratio
Home and 24-h ABPM
Echocardiogram
Holter monitoring in case of arrhythmias
Carotid ultrasound
Peripheral artery/abdominal ultrasound
Pulse wave velocity
Ankle–brachial index
Fundoscopy
Extended evaluation (mostly domain of the specialist)
Further search for cerebral, cardiac, renal and vascular damage, mandatory in resistant and complicated hypertension
Search for secondary hypertension when suggested by history, physical examination or routine and additional tests

ABPM, ambulatory blood pressure monitoring; ECG, electrocardiogram; GFR, glomerular filtration rate.

Figure 8. Laboratory and other investigations in hypertension.

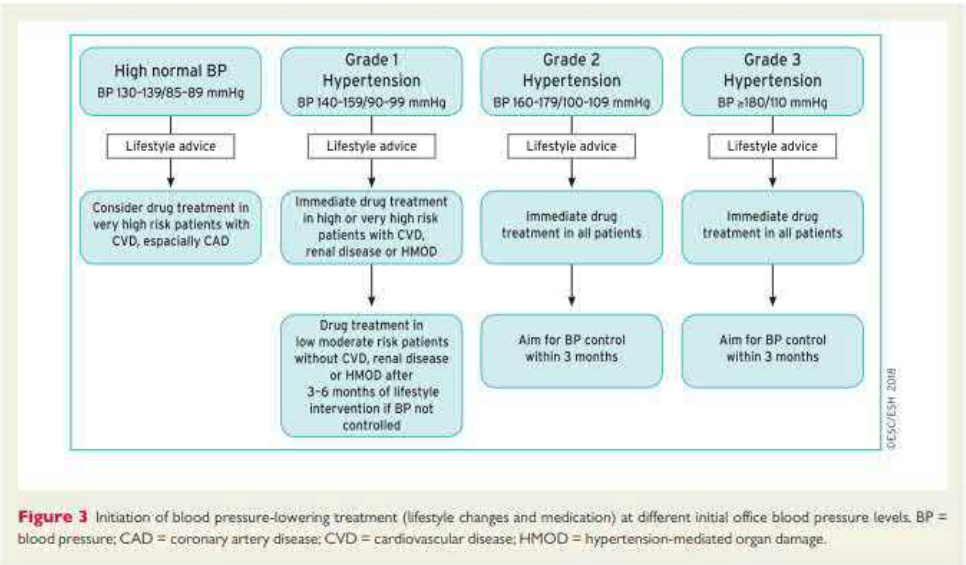

Figure 3 Initiation of blood pressure-lowering treatment (lifestyle changes and medication) at different initial office blood pressure levels. BP = blood pressure; CAD = coronary artery disease; CVD = cardiovascular disease; HMOD = hypertension-mediated organ damage.

Figure 9. Initiation of lifestyle changes and antihypertensive drug treatment.

When to initiate antihypertensive drug treatment?

- Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 hypertension with any level of CV risk, a few weeks after or simultaneously with initiation of lifestyle changes. – class I, level A
- Lowering BP with drugs is also recommended when total CV risk is high because of OD, diabetes, CVD or CKD, even when hypertension is in the grade 1 range. - class I, level A
- In elderly hypertensive patients drug treatment is recommended when SBP is ≥160 mmHg. - class I, level A
- Initiation of antihypertensive drug treatment should also be considered in grade 1 hypertensive patients at low to moderate risk, when BP is within this range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle changes. – class IIa, level B
- Antihypertensive drug treatment may also be considered in the elderly (at least when younger than 80 years) when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated. – class IIb, level C

Special conditions

- In white-coat hypertensives without additional risk factors, therapeutic intervention should be considered to be limited to lifestyle changes only, but this decision should be accompanied by a close follow-up.- class IIa, level C
- In white-coat hypertensives with a higher cardiovascular risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes.- class IIb, level C
- In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a cardiovascular risk very close to that of in-and out-of-office hypertension.

Blood pressure goals

A SBP goal <130 mmHg:

a) is recommended in patients at low–moderate CV risk; I B
b) is recommended in patients with diabetes; I A
c) should be considered in patients with previous stroke or TIA; IIa B
d) should be considered in patients with CHD; IIa B
e) should be considered in patients with diabetic or non-diabetic CKD IIa, B.

Other considerations:

- When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored; IIa, B
- In elderly hypertensives less than 80 years old with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg; I A
- In fit elderly patients less than 80 years old SBP values <140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability; IIb C
- In individuals older than 80 years and with initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions. I B

- A diastolic BP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated. I A

Lifestyle changes

- salt restriction to 5-6 g/day;
- moderation of alcohol consumption to no more than 20–30 g of ethanol per day in men and 10–20 g/day in women;
- high consumption of vegetables and fruits and low fat dairy products;
- reduction of weight to a BMI of 25 kg/m2 and waist circumference to less than 102 cm in men and less than 88 cm in women;
- at least 30 min of moderate dynamic exercise on 5 to 7 days per week.

Compelling and possible contraindications to the use of antihypertensive drugs

Drug	Compelling	Possible
Diuretics	Gout	Metabolic syndrome glucose intolerance; pregnancy; hypercalcaemia; hypokalaemia
β-Blockers	Asthma; A-V block	Metabolic syndrome; glucose intolerance; athletes and physically active patients; chronic obstructive pulmonary disease (except for vasodilator β-blockers)
Calcium antagonists (dihydropyridines)	Tachyarrhythmia; heart failure	
Calcium antagonists (verapamil, diltiazem)	A-V block (Grade 2 or 3, trifascicular block);	severe left ventricular dysfunction; heart failure
ACE inhibitors	Pregnancy; angioneurotic oedema; hyperkalaemia;	Women with childbearing potential bilateral renal artery stenosis
ARBs	Pregnancy; hyperkalaemia; bilateral renal artery stenosis	Women with childbearing potential
Mineralocorticoid receptor antagonists	Acute or severe renal failure (eGFR <30 ml/min); hyperkalaemia	

Drugs to be preferred in specific conditions

Condition		Drug
Asymptomatic organ damage		
	Left ventricular hypertrophy	ACE inhibitor, calcium antagonist, ARB
	Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
	Microalbuminuria	ACE inhibitor, ARB
	Renal dysfunction	ACE inhibitor
Clinical CV event		
	Previous stroke	Any agent effectively lowering BP
	Previous myocardial infarction	BB, ACE inhibitor, ARB
	Angina pectoris	BB, calcium antagonist

	Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
	Aortic aneurysm	BB
	Atrial fibrillation, prevention	Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist
	Atrial fibrillation, ventricular rate control	BB, non-dihydropyridine calcium antagonist

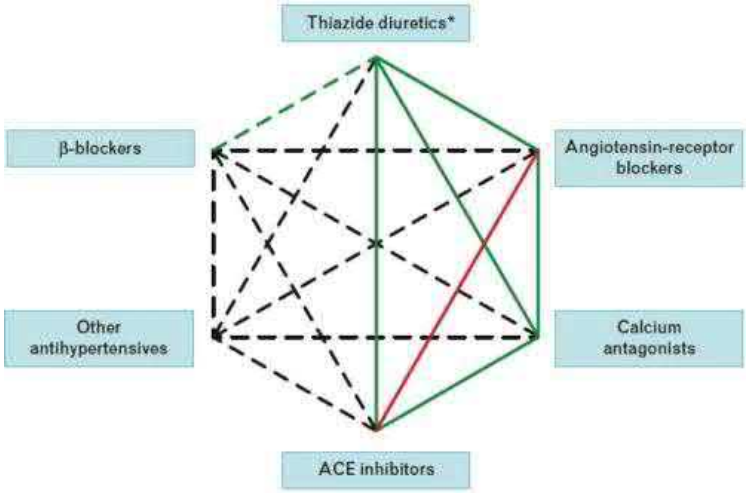

Figure 10. Use combinations!

Diabetes mellitus

One of the most non-communicable diseases. Fourth or fifth leading cause of death in most developed countries. There are more than 177 million people with diabetes worldwide. Incidence of diabetes is increasing- estimated to rise to 300 million to 2025.

Diagnosis of diabetes mellitus

	IFG	IGT	DM
Fasting blood sugar	6.1-7.0 mmol/l	<7.0 mmol/l	≥7.0 mmol/l
Oral glucose tolerance test	<7.8 mmol/l	7.8-11.1 mmol/l	≥11.1 mmol/l
HemoglobinA_{1C}			≥6.5%

IFG: impaired fasting glucose; IGT: impaired glucose tolerance; DM: diabetes mellitus

Lifestyle changes-weight loss

- >20 kg weight loss eliminates diabetes
- Approximately 4 kg weight loss eliminates hyperglicaemia
- Improves coincident risk factors like hypertension and atherogenic lipid profile
- Difficulty in incorporating them into usual lifestyle
- Minor muscular injuries and neuropathy-associated problems (ulcer, foot trauma) may occur

Medical management of hyperglycaemia in type 2 diabetes: based on the recent American Diabetes Association and the European Association for the Study of Diabetes guideline [5].

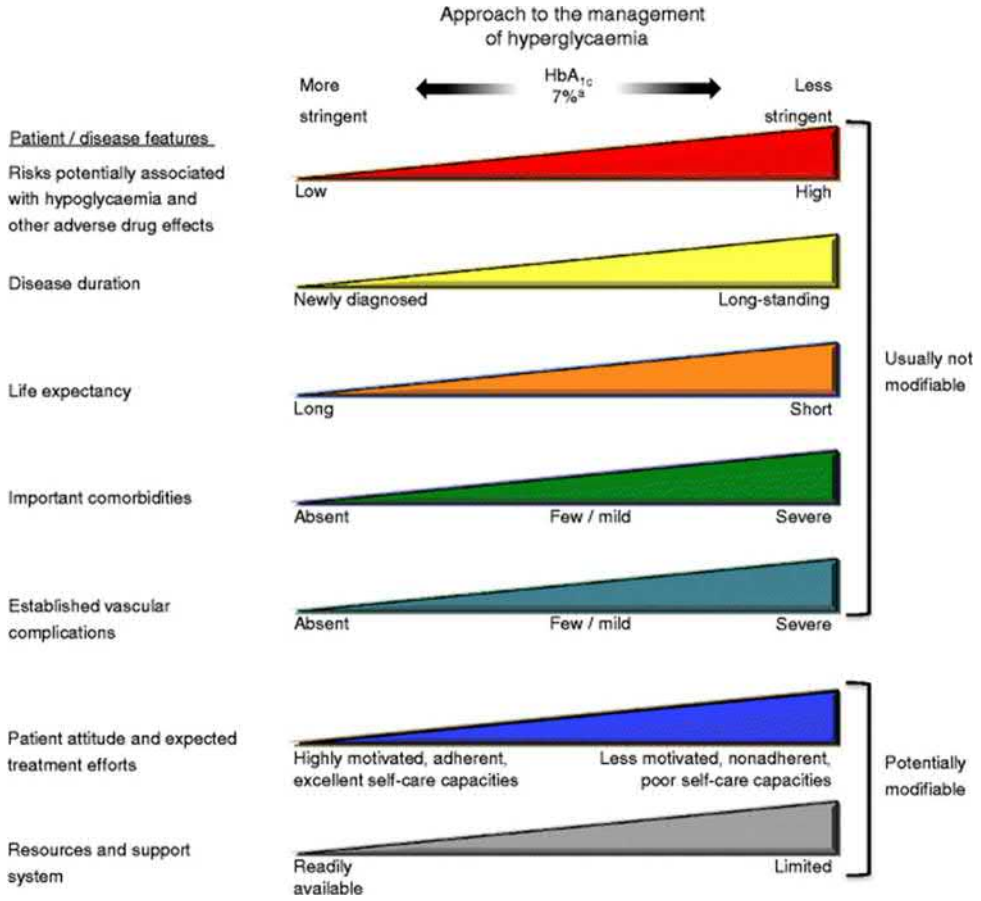

Figure 11. Modulation of the intensiveness of glucose lowering in type 2 diabetes. Depiction of patient and disease factors that may be used by the practitioner to determine optimal HbA1c targets in patients with type 2 diabetes. Greater concerns regarding a particular domain are represented by increasing height of the corresponding ramp. Thus, characteristics/predicaments toward the left justify more stringent efforts to lower HbA1c, whereas those toward the right suggest (indeed, sometimes mandate) less stringent efforts. Where possible, such decisions should be made with the patient, reflecting his or her preferences, needs and values.

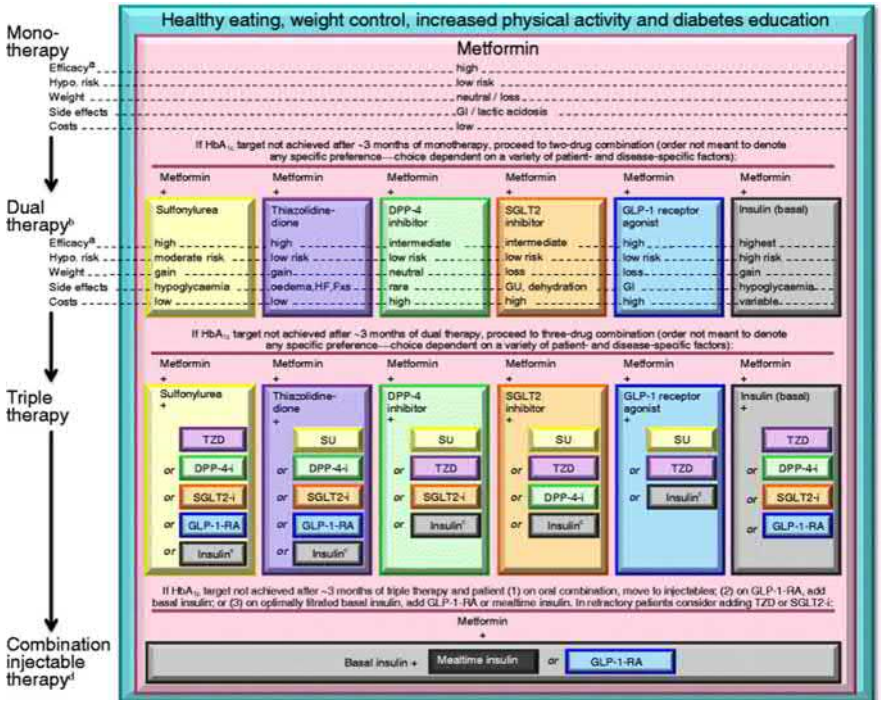

Figure 12. Anti-hyperglycaemic therapy in type 2 diabetes: general recommendations. Potential sequences of anti-hyperglycaemic therapy for patients with type 2 diabetes are displayed, the usual transition being vertical, from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). In most patients, begin with lifestyle changes; metformin monotherapy is added at, or soon after, diagnosis, unless there are contraindications. If the HbA1c target is not achieved after ~3 months, consider one of the six treatment options combined with metformin: a sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist or basal insulin. (The order in the chart, not meant to denote any specific preference, was determined by the historical availability of the class and route of administration, with injectables to the right and insulin to the far right.) Drug choice is based on patient preferences as well as various patient, disease and drug characteristics, with the goal being to reduce glucose concentrations while minimising side effects, especially hypoglycaemia.

Stroke prevention and treatment [6]

Atrial fibrillation (AF) and stroke prevention

AF is associated with a 4-to 5- fold increased risk of ischemic stroke. Ten per cent of strokes are associated with emboli caused by AF. Paroxysmal atrial fibrillation is associated with an increased stroke risk that is similar to that of chronic atrial fibrillation.

Table 1. Stroke risk stratification schemes for patients with atrial fibrillation

$CHADS_2$	**CHA_2DS_2-VASc**
Scoring system • Congestive heart failure – 1 point • Hypertension – 1 point • Age ≥75 y – 1 point • Diabetes mellitus – 1 point • Stroke/TIA – 2 points Risk scores range: 0 – 6 points **Levels of risk for thromboembolic stroke**	**Scoring system** • Congestive heart failure–1 point • Hypertension–1 point • Age 65–74 y–1 point, ≥75 y–2 points • Diabetes mellitus–1 point • Stroke/TIA–2 points

• Low risk for stroke=0 points • Moderate risk=1 point • High risk ≥2 points	• Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque) – 1 point • Female sex – 1 point Risk scores range: 0 – 9 points **Levels of risk for thromboembolic stroke** • Low risk = 0 points • Moderate risk = 1 point • High risk ≥2 points
ACCP treatment guidelines based on estimated risk for thromboembolic stroke	HAS-BLED
• Low risk: no therapy • Moderate risk: OAC • High risk: OAC	• Hypertension – 1 point • Abnormal renal function – 1 point • Abnormal liver function – 1 point • Prior stroke – 1 point • Prior major bleeding or bleeding predisposition – 1 point • INR in therapeutic range <60% of time – 1 point • Age >65 y – 1 point • Use of antiplatelet or nonsteroidal drugs – 1 point • Excessive alcohol use – 1 point • Risk scores range: 0 – 9 points • Score >2 associated with clinically relevant and major bleeding

Recommendations:

1. For patients with valvular AF at high risk for stroke, defined as a CHA2DS2-VASc score of ≥2 and acceptably low risk for hemorrhagic complications, longtermoral anticoagulant therapy with warfarin at a target INR of 2.0 to 3.0 is recommended (*Class I;Level of Evidence A*).
2. For patients with nonvalvular AF, a CHA2DS2-VASc score of ≥2, and acceptably low risk for hemorrhagic complications, oral anticoagulants are recommended (*Class I*). Options include warfarin (INR, 2.0 to 3.0) (*Level of Evidence A*), dabigatran (*Level of Evidence B*), apixaban (*Level of Evidence B*), and rivaroxaban (*Level of Evidence B*). The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including the time that the INR is in therapeutic range for patients taking warfarin.
3. Active screening for AF in the primary care setting in patients >65 years of age by pulse assessment followed by ECG as indicated can be useful (*Class IIa; Level of Evidence B*).
4. For patients with nonvalvular AF and CHA2DS2-VASc score of 0, it is reasonable to omit antithrombotic therapy (*Class IIa; Level of Evidence B*).
5. For patients with nonvalvular AF, a CHA2DS2-VASc score of 1, and an acceptably low risk for hemorrhagic complication, no antithrombotic therapy, anticoagulant therapy, or aspirin therapy may be considered (*Class IIb; Level of Evidence C*). The selection of antithrombotic agent should be individualized on the basis of patient risk factors (particularly risk for intracranial hemorrhage), cost, tolerability, patient preference, potential for drug interactions, and other

clinical characteristics, including the time that the INR is in the therapeutic range for patients taking warfarin.

6. Closure of the LAA may be considered for high-risk patients with AF who are deemed unsuitable for anticoagulation if performed at a center with low rates of periprocedural complications and the patient can tolerate the risk of at least 45 days of postprocedural anticoagulation (Class IIb; Level of Evidence B).

Management of patients with suspected stroke

- Manage ABCs
- Cardiac monitoring
- Intravenous access
- Oxygen (as required O_2 saturation <92%)
- Assess for hypoglycaemia
- Nil per os
- Alert receiving emergency department
- Rapid transport to closest appropriate facility capable of treating acute stroke

Approach to arterial hypertension in acute ischemic stroke

Indication that patient is eligible for treatment with intravenous rtPA or other acute reperfusion intervention

Blood pressure level: systolic >185 mmHg or diastolic >110 mmHg:

- Labetalol 10 to 20 mg iv over 1 to 2 minutes, may repeat one time, or
- Nitropaste 1 to 2 inches, or
- Nicardipine infusion, 5 mg/h, titrate up by 2.5 mg/h at 5-to 15-minute intervals, maximum dose 15 mg/h; when desired blood pressure attained, reduce to 3 mg/h

If blood pressure does not decline and remains >185/110 mmHg, do not administer rtPA.

Tertiary prevention of post-stroke patients

- Blood pressure goal: <140/90 mmHg
- HgA1c goal in diabetes: <6.5%
- Lipid management: Statins in all patients, in the absence of contraindications, irrespective of cholesterol levels, initiated as soon as possible to achieve LDL cholesterol <1.8 mmol/L)
- Aspirin for ever (75-100 mg daily) in all patients without allergy
- Clopidogrel (75 mg daily) in all patients with contraindication to aspirin
- Oral anticoagulant when clinically indicated (e.g. atrial fibrillation)
- Influenza immunization in all patients

Asymptomatic carotid Stenosis: Recommendations

1. Patients with asymptomatic carotid stenosis should be prescribed daily aspirin and a statin. Patients should also be screened for other treatable risk factors for stroke, and appropriate medical therapies and lifestyle changes should be instituted (*Class I; Level of Evidence C*).
2. In patients who are to undergo carotid artery endarteriectomy (CEA), aspirin is recommended perioperatively and postoperatively unless contraindicated (*Class I; Level of Evidence C*).
3. It is reasonable to consider performing CEA in asymptomatic patients who have >70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low (<3%).

However, its effectiveness compared with contemporary best medical management alone is not well established (*Class IIa; Level of Evidence A*).

4. It is reasonable to repeat duplex ultrasonography annually by a qualified technologist in a certified laboratory to assess the progression or regression of disease and response to therapeutic interventions in patients with atherosclerotic stenosis >50% (*Class IIa; Level of Evidence C*).
5. Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum, 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established (Class IIb; Level of Evidence B).
6. In asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS, the effectiveness of revascularization versus medical therapy alone is not well established (Class IIb; Level of Evidence B).
7. Screening low-risk populations for asymptomatic carotid artery stenosis is not recommended (Class III; Level of Evidence C).

Myocardial infarction management [7, 8]

Universal definition of myocardial infarction

Detection of rise and/or fall of cardiac biomarker values (preferably troponin) with at least one value above the 99th percentile of the upper reference limit and with at least one of the following:

- Symptoms of ischaemia;
- New or presumably new significant ST-T changes or new LBBB;
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality;
- Identification of an intracoronary thrombus by angiography or autopsy.

Cardiac death with symptoms suggestive of myocardial ischaemia, and presumably new ECG changes or new LBBB, but death occurring before blood cardiac biomarkers values are released or before cardiac biomarker values would be increased.

Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.

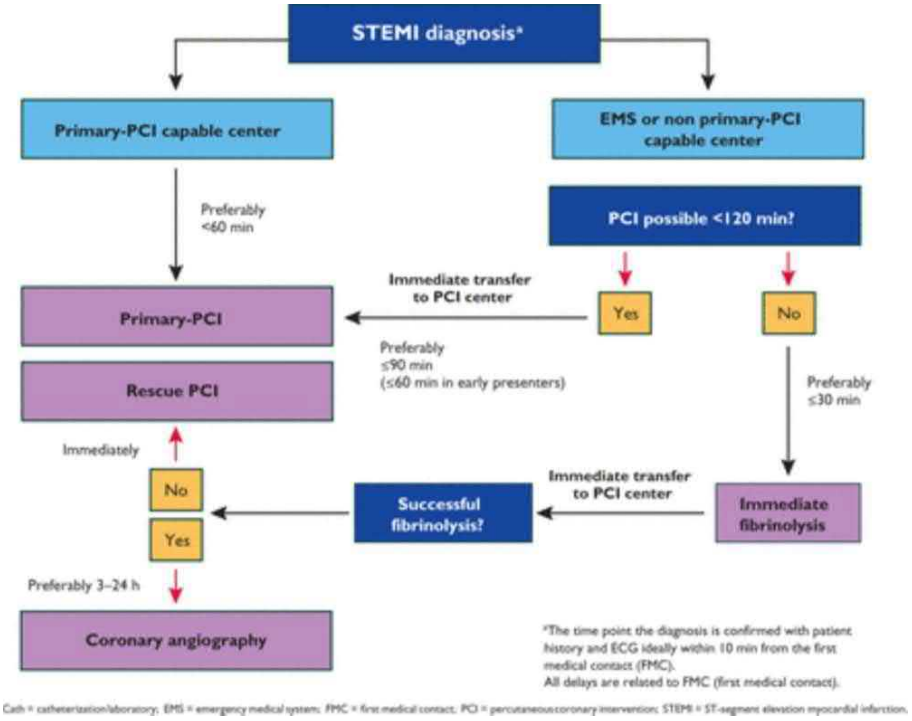

Figure 13. Prehospital and in-hospital management, and reperfusion strategies within 24 h of first medical contact.

Recommendations

- Reperfusion therapy is indicated in all patients with symptoms of <12 h duration and persistent ST-segment elevation or (presumed) new left branch block.
- Reperfusion therapy (preferably primary PCI) is indicated if there is evidence of ongoing ischaemia, even if symptoms may have started >12 h beforehand or if pain and ECG changes have been stuttering.
- Reperfusion therapy with primary PCI may be considered in stable patients presenting 12–24 h after symptom onset.
- Routine PCI of a totally occluded artery >24 h after symptom onset in stable patients without signs of ischaemia (regardless of whether fibrinolysis was given or not) is not recommended.

Relief of pain, breathlessness, and anxiety

Recommendations

- I.v. opioids (4-8 mg morphine) with additional doses of 2 mg at 5-15 min intervals
- O2 (2-4 L/min) if breathlessness or other signs of heart failure
- Tranquillizer-in very anxious patients

Doses of antiplatelet co-therapies

With primary PCI

Aspirin

- Loading dose of 150–300 mg orally or of 80–150 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75–100 mg/day.

Clopidogrel

- Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day.

Prasugrel

- Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day.
- In patients with body weight <60 kg, a maintenance dose of 5 mg is recommended.
- In patients >75 years, prasugrel is generally not recommended, but a dose of 5 mg should be used if treatment is deemed necessary.

Ticagrelor

- Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg b.i.d.

Abciximab

- Bolus of 0.25 mg/kg i.v. and 0.125 µg/kg/min infusion (maximum 10 µg/min) for 12 h.

Eptifibatide

- Double bolus of 180 µg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 µg/kg/min for 18 h.

Tirofiban

- 25 µg/kg over 3 min i.v., followed by a maintenance infusion of 0.15 µg/kg/min for 18 h.

With fibrinolytic therapy

Aspirin

- Starting dose 150–500 mg orally or i.v. dose of 250 mg if oral ingestion is not possible.

Clopidogrel

- Loading dose of 300 mg orally if aged ≤75 years, followed by a maintenance dose of 75 mg/day.

Without reperfusion therapy

Aspirin

- Starting dose 150–500 mg orally.

Clopidogrel

- 75 mg/day orally.

Doses of antithrombin co-therapies

With primary PCI

Unfractionated heparin

- 70–100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned.
- 50–60 U/kg i.v. bolus with GP IIb/IIIa inhibitors.

Enoxaparin

- 0.5 mg/kg i.v. bolus.

Bivalirudin

- 0.75 mg/kg i.v. bolus followed by i.v infusion of 1.75 mg/kg/h for up to 4 h after the procedure as clinically warranted. After cessation of the 1.75 mg/kg/h infusion, a reduced infusion dose of 0.25 mg/kg/h may be continued for 4–12 h as clinically necessary.

With fibrinolytic therapy

Unfractionated heparin

- 60 U/kg i.v. bolus with a maximum of 4000 U followed by an i.v. infusion of 12 U/kg with a maximum of 1000 U/h for 24–48 h. Target aPTT: 50–70 s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24 h.

Enoxaparin

- In patients <75 years of age: 30 mg i.v. bolus followed 15 min later by 1 mg/kg s.c. every 12 h until hospital discharge for a maximum of 8 days The first two doses should not exceed 100 mg.
- In patients >75 years of age: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg for the first two s.c. doses.
- In patients with creatinine clearance of <30 mL/min, regardless of age, the s.c. doses are given once every 24 h.

Fondaparinux

- 2.5 mg i.v. bolus followed by a s.c. dose of 2.5 mg once daily up to 8 days or hospital discharge.

Without reperfusion therapy

Unfractionated heparin, enoxaparine, fondaparinux:

- Same dose as with fibrinolytic therapy.

Routine therapies in the acute, subacute and long term phase of ST-segment elevation myocardial infarction

Recommendations

- Active smokers with STEMI must receive counselling and be referred to a smoking cessation programme.
- Each hospital participating in the care of STEMI patients must have a smoking cessation protocol.
- Exercise-based rehabilitation is recommended.
- Antiplatelet therapy with low dose aspirin (75–100 mg) is indicated indefinitely after STEMI.
- In patients who are intolerant to aspirin, clopidogrel is indicated as an alternative to aspirin
- Dual antiplatelet therapy (DAPT) with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI.
- DAPT with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of:
    - 1 month for patients receiving bare metal stent
    - 6 months for patients receiving drug eluting stent
- In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months.
- In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA2DS2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy.

- If patients require triple antithrombotic therapy, combining DAPT and OAC, e.g. because of stent placement and an obligatory indication for OAC, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk.
- In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk.
- DAPT should be used up to 1 year in patients with STEMI who did not receive a stent.
- Gastric protection with a proton pump inhibitor should be considered for the duration of DAPT therapy in patients at high risk of bleeding.
- Oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all STEMI patients without contraindications.
- Oral treatment with β-blockers is indicated in patients with heart failure or LV dysfunction.
- Intravenous beta-blockers must be avoided in patients with hypotension or heart failure.
- Intravenous beta-blockers should be considered at the time of presentation in patients without contraindications, with high blood pressure, tachycardia and no signs of heart failure.
- A fasting lipid profile must be obtained in all STEMI patients, as soon as possible after presentation.
- It is recommended to initiate or continue high dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values.
- Reassessment of LDL-cholesterol should be considered after 4–6 weeks to ensure that a target value of ≤1.8 mmol/L (70 mg/dL) has been reached.
- Verapamil may be considered for secondary prevention in patients with absolute contraindications to beta-blockers and no heart failure.
- ACE inhibitors are indicated starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct.
- An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors.
- ACE inhibitors should be considered in all patients in the absence of contraindications.
- Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalaemia.

Peripheral arterial disease [9, 10]

Prognosis of peripheral artery disease (PAD)

Mortality:

- 55% coronary artery disease
- 10% cerebral artery disease
- 25% non-vascular diseases
- <10% other vascular diseases

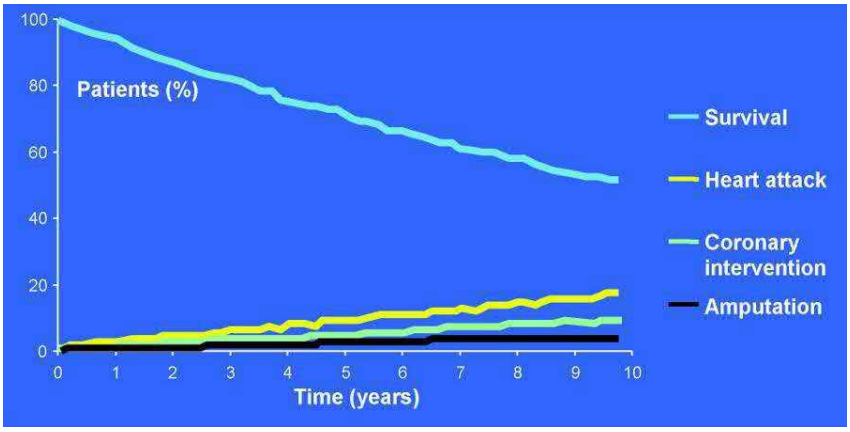

Figure 14. Cardiovascular mortality of patients with peripheral arterial disease

Table 2. 5-year mortality of different diseases

Disease	Patients (%)
Breast cancer	15
Hodgkin disease	18
Peripheral Artery Disease (PAD)	28
Colorectal cancer	38
Lung cancer	86

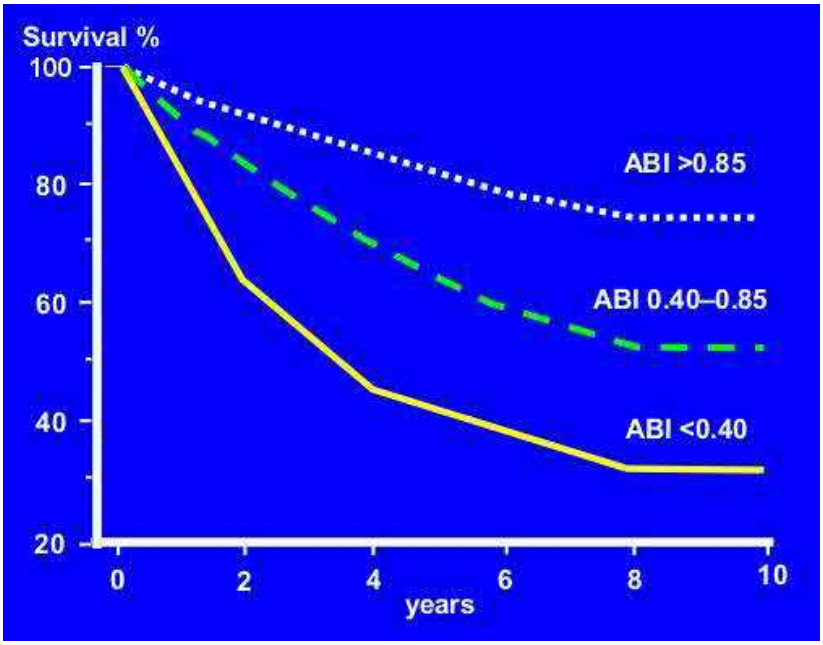

Figure 15. The mortality is connected to the severity of PAD [11]

Classification

Table 3. The Fontaine classification

Fontaine Stage	Symptoms
I.	Asymptomatic
II. a.	Mild CI
II. b.	Moderate-severe CI
III.	Rest pain
IV.	Ulcer/gangrene

Table 4. The Rutherford classification

Rutherford grade	Category	Symptoms
0	0	Asymptomatic
I.	1.	Mild intermittent claudication
I.	2.	Moderate intermittent claudication
I.	3.	Severe intermittent claudication
II.	4.	Rest pain
III.	5.	Mild tissue damage
IV.	6.	Severe tissue damage

Diagnosis of PAD

Anamnesis

- Family, personal
- Risk factors (smoking, hypertension, DM)
- Typical symptoms: intermittent claudication

Physical examination - palpation and auscultation of arteries
Non-invasive diagnostics: ankle-brachial index, duplex ultrasound, MR/CT angiography
Invasive diagnostics- angiography

Ankle-brachial index (ABI) measurement

- Simple, cheap, non-invasive, high sensitivity and specificity
- Stenosis above 50%: sensitivity approx. 90%, specificity approx. 98%
- Pathological range = progressed vascular disease
- Predictive value is proven

Figure 16. Doppler device for ABI measurement

Measurement of ABI:

$$ABI = \frac{\text{higher ankle systolic blood pressure}}{\text{brachial systolic blood pressure}}$$

Evaluation:

- Healthy: 1-1.3
- Pathological ≤0.9
- Severe ≤0.4
- Non-compressible >1.3

Treatment of PAD

- Aim: the prevention and treatment of local and systemic events
- Conservative: lifestyle changes, pharmacologic treatment
- Interventional radiology
- Surgery

Lifestyle changes

- Stop smoking
- Decrease obesity
- Proper diet
- Regular physical activity, walking practices

Aspects of the treatment of hypertension in PAD

- To reach the optimal target value to prevent cardiovascular events
- To maintain enough perfusion of the limb for the better local outcome

Pharmacological therapy of hypertension in PAD

Blockade of the renin-angiotensin-aldosteron system

- ACE inhibitors

- AT1 receptor blockers

Calcium channel antagonists

Beta-adrenergic blocking drugs: not contraindicated, but only if other indication is present (IHD, angina pectoris, arrhythmia, heart failure)

- Carvedilol
- Nebivolol

Other antihypertensive drugs

- Alpha-1-adrenergic receptor blocker: not recommended in case of LV dysfunction
- Imidazoline receptor agonists
- Diuretics

Diabetes mellitus in peripheral arterial disease

Good metabolic control! HBA1c <6.5%.

Special beneficial vascular effects:

Gliclazide

- antioxidant effect

Tiazolidindions (pioglitazone)

- Nuclear PPARγ receptor agonist effect
- Direct vascular effect: inhibition of the migration and proliferation of vascular cells

Dyslipidaemia

Statins

- Decreasing LDL cholesterol + pleiotropic effect
- NOS activity increases
- Cell migration and proliferation decreases
- Target value of ≤1.8 mmol/L (70 mg/dL)

Fibrates

- Decreasing fibrinogen and PAI-1
- In case of low HDL cholesterol, normal LDL cholesterol and elevated triglycerides

Antiplatelet and antithrombotic drugs

- Aspirin, in daily doses of 75-325 mg, is recommended as safe and effective antiplatelet therapy to reduce the risk of MI, stroke, or vascular death.
- Clopidogrel (75 mg/d) is recommended as an effective alternative antiplatelet therapy to aspirin.

Thrombolysis

- Catheter-based thrombolysis is an effective and beneficial therapy and is indicated for patients with acute limb ischemia of less than14 days' duration. Mechanical thrombectomy devices can be used as adjunctive therapy for acute limb ischemia.

Other pharmacological treatments

- Vasoactive drugs (cilostasol, pentoxifyllin, naftidrofuryl, L-carnitin)
- Prostaglandins (alprostadil, iloprost)

- Stem cell therapy

Summary

- Primary prevention of CV risk factors and diseases is fundamental part of family medicine.
- Secondary prevention- screening and early diagnosis are needed for proper treatment.
- Tertiary prevention - in collaboration with specialists to avoid complications and recurrent MI/stroke, must be based on current guidelines.

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Depression in Family Practice
Peter Torzsa MD, PhD

Depression is a common mental disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration.

Depression is the most common psychiatric disorder in the general population and the most common mental health condition in patients seen in primary care. Although symptoms of depression are prevalent among primary care patients, few patients discuss these symptoms directly with their primary care clinicians. Instead, two-thirds of primary care patients with depression present with somatic symptoms (e.g., headache, back problems, or chronic pain), making detection of depression more difficult. It is estimated that only 50 percent of patients with major depression are identified [1].

Unless directly asked about their mood, patients omit information about depressive symptoms for a variety of reasons, including fear of stigmatization, belief that depression falls outside the purview of primary care, belief that depression isn't a "real" illness, concerns about medical record confidentiality, and concerns about being prescribed antidepressant medication or being referred to a psychiatrist[2].

Untreated depression is associated with:

- Increased risk of suicide [3]
- Decreased quality of life [4]
- Increased risk of mortality (relative risk, RR: 1.81) [5]
- Poor physiological outcomes when depression co-occurs with chronic medical conditions [6]

DEFINITIONS
Depressive syndromes are defined in the Diagnostic and Statistical Manual of Mental [Disorders, 5th Edition (DSM-5). The term "major depression" in this topic refers to unipolar depression.

Criteria for Major Depressive Disorder
- Symptoms should be present for at least two weeks in a persistent fashion.
- Five symptoms are needed.

At least one must be one of the two main features:
- Persistent sad mood (most of the day on most days)
- Loss of interest or pleasure (anhedonia). Either by subjective report or observations of others.

The remainder can be from the following symptoms (on most days):
- Increase or decrease in appetite or weight
- Increase or decrease in sleep duration
- Psychomotor agitation or retardation
- Fatigue
- Worthlessness or guilty feelings
- Difficulty concentrating or indecisiveness

- Recurrent thoughts of death or suicidal thoughts or plans
- “Spontaneous” depression

Epidemiology and risk factors

Depression is highly prevalent throughout the world, and the prevalence appears to be increasing. Depression is more difficult to detect in cultures where patients are more likely to present with somatic symptoms rather than emotional symptoms.

In the United States, the National Comorbidity Survey Replication found an annual prevalence rate for major depressive disorder (MDD) of 6.7% and a lifetime prevalence rate of 16.5% [7, 8]. The prevalence of MDD in Hungary can be found in Table 1.

Table 1. The International and Hungarian prevalence of MDD

Prevalence	Lifetime (%)	1 year (%)	1 month (%)
International data			
Major depression	4.6-15.7	3.4-5.2	1.5-5.2
Bipolar depression	0.5-5.5	0.3-1.7	0.1-0.6
National data			
Major depression	15.1	7.1	2.6
Bipolar depression	5.1	1.1	0.5

Among patients with chronic medical illness, the annual prevalence rate is significantly higher, approximately 25 percent. Rates of depression may be particularly high in diseases of the central nervous system (eg, stroke, traumatic brain injury, Parkinson disease), cardiovascular disorders, cancer, and conditions involving immune and inflammatory mechanisms (eg, systemic lupus erythematosus).

Risk factors for depression

- Female gender
- Prior depressive episode
- Positive family history
- Childbirth (i.e., postpartum depression)
- Childhood trauma
- Stressful life events
- Poor social support
- Serious medical illness
- Dementia
- Substance abuse

By using the columns of Table 2, the severity of depression can be determined.

Table 2. Depression severity criteria

A	B
• Depressed mood	• Reduced self esteem and confidence • Ideas of guilt and unworthiness

• Loss of interest and enjoyment in usual activities • Reduced energy and decreased activity	• Pessimistic thoughts • Disturbed sleep • Diminished appetite • Ideas of self harm

The severity of depressive episode

Mild: > 1 from column A plus 1-2 from column B. Or 5-6 sx but mild in severity and functional impairment.

Moderate: > 1 from column A plus 2-3 from column B. Or 7 – 8 sx but moderate functional impairment.

Severe: All 3 from column A plus > 3 from column B. Or fewer sx but any of these: severe functional impairment, psychotic sx, recent suicide attempt, or has specific suicide plan or clear intent.

69% of diagnosed depressed patients reported unexplained physical symptoms as their chief compliant. The emotional and physical symptoms of depression can seen in Table 3.

Table 3. Emotional and physical symptoms of depression

Emotional symptoms include:	Physical symptoms include:
• Sadness • Loss of interest or pleasure • Overwhelmed • Anxiety • Diminished ability to think or concentrate, indeciveness • Excessive or inappropriate guilt	• Vague aches and pains • Headache • Sleep disturbances • Fatigue • Back pain • Significant change in appetite resulting in weight loss or gain

Possible causes of depression

- Stressful event, life change
- Death, divorce, job loss, major illness
- Even happy events can be stressful
- Marriage, parenthood, new job
- Chronic stress
- Poverty, war, sexual abuse, anxiety
- Chronic disease, chronic pain
- Adolescence
- Social defeat stress
- Other causes of depression
- Genetic: depression runs in families
- Gender/hormones: women are more likely to get depressed
- Child birth
- Head injury
- Endocrine disorders (hypothyroidism)
- AIDS

The first depression is usually triggered by stress of some sort. After several depressions (usually >4), new episodes may occur without any obvious trigger. The more depressions, the more likely this will occur.

List of risk factors for suicide

- Elderly (>60 years)
- Male (female-male, 2-2,5:1)
- Caucasian
- Living alone
- Prior suicide attempt
- Family history of suicide
- Medically ill
- Psychosis
- Alcohol or other substance abuse

Older males are at higher risk for suicide than any other demographic group, and they tend to use violent methods (such as a gun) that often result in completed suicide. Although suicide and attempted suicide are relatively rare events, depression, the major cause of suicide, is common in primary care. Up to 60% and 40% respectively of suicide victims contact their GPs 4 weeks and 1 week before the death. Many attenders consult for other reasons. Many people do not readily present depression or suicidal ideas or intent in primary care, so a high index of suspicion is needed, especially in high risk groups.

Screening instruments

A number of attributes should be considered in choosing a questionnaire to screen for depression, including its diagnostic accuracy in the population being screened and the feasibility of its administration. Factors impacting feasibility include the number of questions, scoring and ease of interpretation, and reading level required. These characteristics are summarized in a table about recommended questionnaires.

The Beck Depression Inventory for Primary Care

The BDI-PC is a nine-item scale adapted from the extensively validated 21-item Beck Depression Inventory (BDI-II). The 21-item BDI-II is useful for monitoring treatment response. In primary care outpatients, the BDI-PC with a cutoff of four points had 97 percent sensitivity and 99 percent specificity for identifying major depression.

Risk assessment and monitoring

Always ask people with depression directly about suicidal ideation and intent.

If there is a risk of self-harm or suicide:

- assess whether the person has adequate social support and is aware of sources of help
- arrange help appropriate to the level of need
- advise the person to seek further help if the situation deteriorates.

If a person with depression presents considerable immediate risk to themselves or others, refer them urgently to specialist mental health services. Advise people with depression of the potential for increased agitation, anxiety and suicidal ideation in the initial stages of treatment.

Check if they have any of these symptoms and:

- ensure that the person knows how to seek help promptly
- review the person's treatment if they develop marked and/or prolonged agitation.

Advise a person with depression and their family or carer to be vigilant for mood changes, negativity and hopelessness, and suicidal ideation, and to contact their practitioner if concerned. This is particularly important during high-risk periods, such as starting or changing treatment and at times of increased personal stress.

If a person with depression is assessed to be at risk of suicide:

- take into account toxicity in overdose if an antidepressant is prescribed or the person is taking other medication; (if necessary, limit the amount of medicine available)
- consider increasing the level of support, such as more frequent direct or telephone contacts (Lelki Elsősegély Szolgálat in Hungary, Tel: 116-123
- consider referral to specialist mental health services.

When offering a person antidepressant medication:

- explain the reasons for offering it
- discuss the risks and benefits
- discuss any concerns they have about taking the medication
- ensure they have information to take away that is appropriate for their needs.

When prescribing antidepressant medication, give people information about:

- how long it takes (typically 2–4 weeks) to begin to start to feel better
- how important it is to follow the instructions on when to take antidepressant medication
- how treatment might need to carry on even after remission
- how they may be affected when they first start taking antidepressant medication, and what these effects might be
- how they may be affected if they have to take antidepressant medication for a long time and what these effects might be, especially in people over 65
- how taking antidepressant medication might affect their sense of resilience (how strong they feel and how well they can get over problems) and being able to cope
- how taking antidepressant medication might affect any other medicines hey are taking
- how they may be affected when they stop taking antidepressant medication, and how these effects can be minimised
- the fact that they cannot get addicted to antidepressant medication.

There is some evidence that mental health training for GPs may be linked to the reduction of depressive suicides.

Advise people taking antidepressant medication, if they stop taking it, miss doses or don't take a full dose, they may have discontinuation symptoms such as:

- more mood changes
- restlessness
- problems sleeping
- unsteadiness
- sweating

- abdominal symptoms
- altered sensations.

First-line treatment for depression

Lower intensity psychological interventions

Modern psychotherapy

- Focusing on abnormal thinking (e.g. extreme pessimism and hopelessness in depression) – COGNITIVE-BEHAVIOR THERAPY
- Focusing on human relationships (e.g. dispute, role changes, grief, communication skills) – INTERPERSONAL PSYCHOTERAPY
- provide age-appropriate, written, audio or digital (computer or 6 online) material

Non pharmacological treatment

- Physical activity programmes which consist of 45 minutes of aerobic exercise of moderate intensity and duration twice a week for 5 weeks, then once a week for a further 7 weeks. It is delivered in groups by a competent practitioner.

Modern social therapy

- Case manager that helps the patient in everyday activity
- Sheltered houses
- Supported employment
- Daytime “hospitals” and clubs
- Social skill training

Pharmacological treatment

Currently available antidepressants and their recommended doses can be found in Table 4.

Table 4. The currently available antidepressants and their recommended doses [9]

Currently available antidepressants and their recommended dosages. SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; MAO I, monoamine oxidase inhibitor. A generic formulation is available. Approved by the Food and Drug Administration (FDA) for treatment of obsessive-compulsive disorder, but not depression. "The higher dosage is approved in some countries but not in the USA. §A maximum therapeutic dose has not yet been established for this compound. Even higher doses might be indicated if plasma drug concentrations are low (ie, <50 ng/mL). The maximum FDA-approved dosage of the extended-release formulation is 225 mg day.

Drug name	Initial dose (mg day)	Modal therapeutic dose (mg day)	Maximum dosage (mg day)
SSRIS*			
• Fluoxetine	20	20-40	60-80
• Paroxetine	20	30	50
• Fluvoxamine	50	150	300
• Citalopram	20	30	40-60+
• Escitalopram	10	20	20§
TCAs and related compounds			
• Amitriptyline	25	150	300
• Nortriptyline	25	50-75	100-150
• Imipramine	25	150	300
• Desipramine	25	100	300
• Doxepin	25	100	300

• Clomipramine • Protriptyline • Trimipramme	25 10 25-50	100 20-30 150	300 60 300

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Diabetes Mellitus

László Kalabay MD, PhD

In this chapter the definition, epidemiology, pathogenesis are briefly mentioned. We focus on the tasks of the General Practitioner on the diagnosis, treatment, and management of patients with diabetes, especially on those with type 2 diabetes mellitus.

Definition

DM is a group of common metabolic disorders characterized by reduced insulin secretion, decreased glucose utilization and increased glucose production.

Epidemiology

The frequency varies with age and geographical regions.

Prevalence:

- <20 years: 0,19%
- >20 years: 8,6%
- 65 years: 20,1%

In the USA: African Americans 13%, 10.2% in Hispanic Americans 10.2%, Native Americans: 15.5%, non-Hispanic whites 7.8%

Incidence:

- Finland: 35/100,000
- Pacific Japan and China: 1-3/100,000
- Northern Europe, USA: 8-17/100,000

Diabetes mellitus is the leading cause of: end-stage renal disease (ESRD), non-traumatic lower extremity amputations, and adult blindness.

Spectrum of glucose homeostasis and diabetes mellitus

It is very important to be familiar with the spectrum and glucose homeostasis

		Hyperglycemia			
	Normal glucose tolerance	**Impaired fasting glucose or impaired glucose tolerance**	**Diabetes mellitus**		
Type of diabetes			**Not insulin requiring**	**Insulin required for control**	**Insulin required for survival**
Type 1	not reversible				
Type 2	may be reversible				
Other specific types	not reversible				
Gestational diabetes	may be reversible				

Time (years)	→		
FPG (mg/dL) (mM/L)	<110 6.1	110-125 6.1-6.9	≥126 ≥7.0
2h OGTT (mg/dL) mM/L	<140 7.8	140-199 7.7-11	≥200 ≥11
HbA1C	<5.6%	5.7-6.4%	≥6.5%

FPG: Fasting plasma glucose; OGTT: oral glucose tolerance test.

Source: Harrison's Principles of Internal Medicine, 20th Edition (Eds. Eds. Kasper DL, Fauci AS, Hauser S, et al.) McGraw-Hill (2018)

Etiologic classification of diabetes mellitus

I. Type 1 diabetes (T1DM)

Characterized by β-cell destruction, usually leading to absolute insulin deficiency. Can be autoimmune or idiopathic. Genes associated with T1DM: HLA DR3 and DR4, DQA1*0301, DQB1*0302, DQA1*501, DQB1*0201. Protective genes: DQA1*0102, DQB1*0602. Islet cell autoantibodies: glutamic acid decarboxylase (GADA), islet cell antibody (ICA), islet ganglioside, carboxypeptidase H, or idiopathic. The presence of GADA and ICA helps differentiate T1DM from T2DM. The disease usually starts prior to age 30, lean body habitus, requirement of insulin as the initial therapy, propensity to develop ketoacidosis, an increased risk of other autoimmune disorders such as autoimmune thyroid disease, adrenal insufficiency, pernicious anemia, and vitiligo.

II. Type 2 diabetes (T2DM)

Characterized by insulin resistance of peripheral tissues. relative, later absolute insulin deficiency to a predominantly insulin secretory defect with insulin resistance. Genetic predisposition is very strong, polygenic and multifactorial. T2DM usually develops after the age of 30, are usually obese (80% are obese, but elderly individuals may be lean), may not require insulin therapy initially, may have associated conditions such as insulin resistance, hypertension, cardiovascular disease, dyslipidemia, or polycystic ovarian syndrome (PCOS), insulin resistance is often associated with abdominal obesity and hypertriglyceridemia. Although most individuals diagnosed with T2DM are older, the age of diagnosis is declining. T2DM with obesity is by far the most common form of diabetes. Pathophysiology includes impaired insulin secretion, peripheral insulin resistance, and excessive hepatic glucose production. Risk factors for T2DM are:

- Family history of diabetes (i.e., parent or sibling with T2DM)
- Obesity (BMI ≥ 25 kg/m^2)
- Habitual physical inactivity
- Race/ethnicity (e.g., African American, Hispanic American, Native American, Asian American, Pacific Islander)
- Previously identified IFG or IGT
- History of GDM or delivery of baby >4 kg
- Hypertension (blood pressure ≥ 140/90 mmHg)
- HDL cholesterol level ≤ 35 mg/dL (0.90 mmol/L) and/or a triglyceride level ≥250 mg/dL (2.82 mmol/L)
- Polycystic ovary syndrome or acanthosis nigricans

- History of vascular disease

III. Other specific types of diabetes

- Genetic defects of β-cell function and insulin action: MODY 1-6, mitochondrial DNA, lipodystrophy, etc.
- Diseases of the pancreas: pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy
- Endocrinopathies: acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
- Drug- or chemical-induced: glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, phenytoin, α-interferon, protease inhibitors, clozapine, β-blockers
- Infections: congenital rubella, cytomegalovirus, coxsackie
- Other rare causes: “stiff-man” syndrome, anti-insulin receptor antibodies
- Other rare genetic diseases that may be associated with diabetes: Down's syndrome, Klinefelter's syndrome, Turner's syndrome, porphyria, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, Prader-Willi syndrome, etc.

IV. Gestational diabetes mellitus (GDM)

Occurs during pregnancy and subsides after delivery. Gestational diabetes occurs when a woman's pancreatic function is not sufficient to overcome both the insulin resistance created by the anti-insulin hormones secreted by the placenta during pregnancy (e.g., estrogen, prolactin, human chorionic somatomammotropin, cortisol, and progesterone) and the increased fuel consumption necessary to provide for the growing mother and fetus. Since there is a progressive impairment of the β-cell function in GDM it usually returns during the following pregnancies and may transform to permanent diabetes.

Criteria for the diagnosis of diabetes mellitus

1. HBA1C ≥6.5%[a*]
2. Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)[b]
3. Two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[c]
4. Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)[d]

a According to the 2018 American Diabetes Association (ADA) recommendations
b Fasting is defined as no caloric intake for at least 8 h
c The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use
d Random is defined as without regard to time since the last meal
*In the absence of unequivocal hyperglycemia, criteria 1 to 3 should be confirmed by repeat testing.

Source: Modified from American Diabetes Association (ADA)

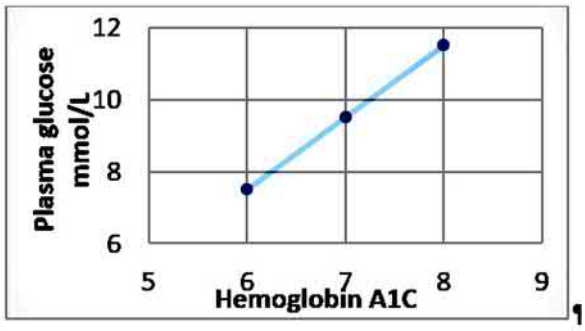
Forms of glucose tolerance

- FPG < 5.6 mmol/L (100 mg/dL): normal
- FPG 5.6-7.0 mmol/L (100-126 mg/dL): IFG
- FPG ≥ 7.0 mmol/L (126 mg/dL): DM.
- Plasma glucose levels between 7.8-11.1 mmol/L (140-200 mg/dL) 2 h after a 75 g oral glucose load: IGT
- Individuals with IFG or IGT are at substantial risk for developing T2DM (40% risk over the next 5 years) and cardiovascular disease.

Further laboratory assessment

- Hemoglobin A1C
- C-peptide
- Microalbuminuria, se. creatinine/microalbumin
- Serum lipid levels
- Thyroid dysfunction
- Islet cell antibodies (ICA, GADA)
- Echocardiography, ergometry, carotid USG in patients with high-risk for coronary disease

Glycation products in DM



- Glycated hemoglobin Hemoglobin A1C: 120 days. 1% change = 35 mg/dl (1.9 mmol/L) plasma glucose
- Fructosamine: 2 weeks

Screening for diabetes mellitus

(Recommendation of the American Diabetes Association (ADA)

- Determination of FPG recommends screening all individuals >45 years every 3 years
- Screening individuals with additional risk factors at an earlier age.
- At the 24th week of gestation (for GDM)
- Insulin resistance syndromes

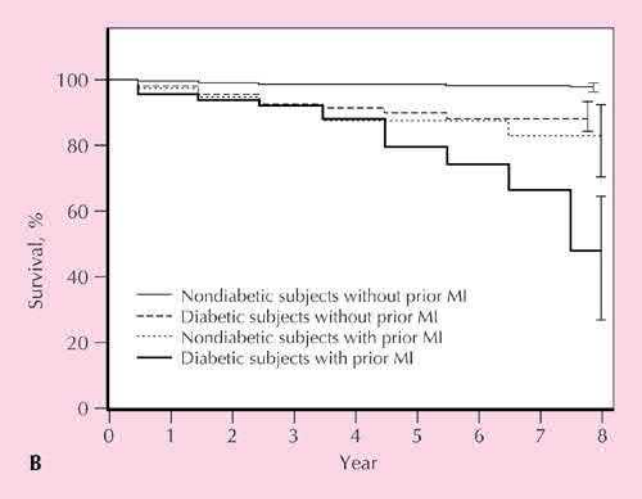
Metabolic syndrome

- central or visceral obesity (abdominal circumference)
- and 2 of the followings: hypertension, hypercholesterinemia, decreased HDL, elevated triglycerides, type 2 diabetes or IGT/IFG

Rare forms: acanthosis nigricans, PCOS

Importance: hyperinsulinemia → accelerated cardiovascular disease

Principles of long-term treatment of DM



Source: ImagesMD

This figure shows that the long-term survival of patients with T2DM does not differ from that of non-diabetic individuals with myocardial infarction. Thus **all patients with T2DM should be considered as patients with myocardial infarction!**

The goals of therapy:

1. Eliminate symptoms related to hyperglycemia. Symptoms usually resolve when the plasma glucose is <11.1 mmol/L (200 mg/dL)
2. Reduce or eliminate the long-term microvascular and macrovascular complications of DM
3. Allow the patient to achieve as normal a lifestyle as possible.

Optimal diabetes therapy involves more than plasma glucose management

Members of the health care team are: primary care provider, endocrinologist or diabetologist, certified diabetes educator, nutritionist

When the complications of DM arise: neurologist, nephrologist, vascular surgeon, cardiologist, ophthalmologist, and podiatrist

Management of DM

- Patient education
- Diet, lifestyle
- Insulin therapy
- Oral antidiabetic drugs (glucose-lowering agents)
- Screening for complications
- Special conditions and aspects

Topics for the education of the patient with DM

- Self-monitoring of blood glucose
- Urine ketone monitoring (T1DM)
- Insulin administration

Guidelines for diabetes management during illnesses

- Management of hypoglycemia
- Foot and skin care

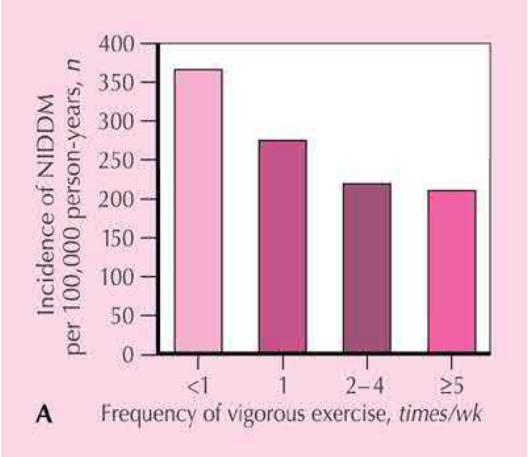
- Diabetes management before, during, and after exercise
- Risk factor-modifying activities

Nutritional recommendations for all persons with diabetes

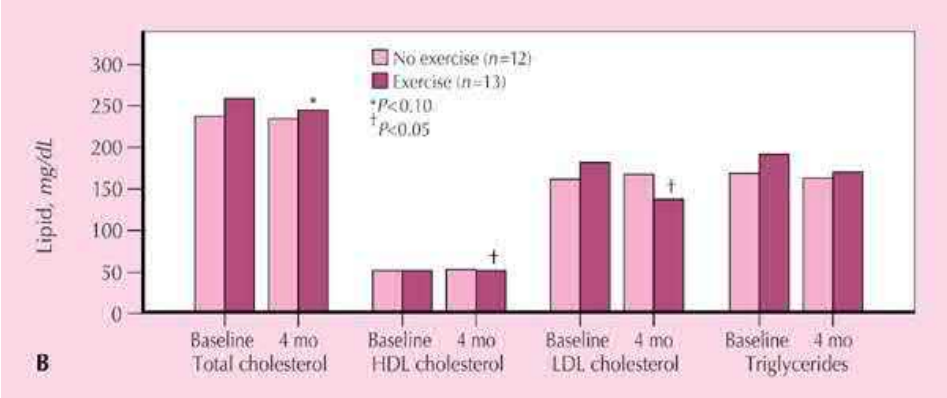
- Protein: ~15-20% of kcal/d (~10% for those with nephropathy)
- Saturated fat: <10% of kcal/d (<7% for those with elevated LDL)
- Polyunsaturated fat: ~10% of kcal; avoid trans-unsaturated fatty acids
- 60–70% of calories to be divided between carbohydrate and monounsaturated fat, based on medical needs and personal tolerance. Glucose: 140-220 g/die
- Fiber (20-35 g/d) and sodium (≤3 g/d) as recommended for the general healthy population
- Cholesterol intake ≤300 mg/d
- Alcohol worsens diabetes
- Weight loss is desired in obese patients with T2DM

The benefits of physical exercise in DM

Exercise is a central treatment modality for T2DM. Its benefits are: cardiovascular risk reduction, reduced blood pressure, maintenance of muscle mass, reduction in body fat, weight loss, lowering plasma glucose (during and following exercise), increasing insulin sensitivity.



Source: Images MD



Source: Images MD

The ideal goals for glycemic control

Index	Goal
Preprandial plasma glucose*	5.0-7.2 mmol/L (90-130 mg/dL)
Peak postprandial plasma glucose	<10 mmol/L (<180 mg/dL)
A1C	5-7%

*Plasma glucose values are 10–15% higher than whole blood values.

Source: Harrison's Principles of Internal Medicine, 17th Edition (Eds. Fauci AS, Braunwald, E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalso J.), McGraw-Hill (2008)

Properties of insulin preparations

	Time of action		
Preparation	**Onset, h**	**Peak, h**	**Effective duration, h**
Short acting			
Lispro	<0.25	0.5-1.5	3-4
Insulin aspart	<0.25	0.5-1.5	3-4
Regular	0.5-1.0	2-3	3-6
Long-acting			
Detemir	1-4	__a	Up to 24
Glargine	1-4	__a	Up to 24
NPH	1-4	6-10	10-16
__a Glargine and detemir have minimal peak activity.			
Combinations			
75/25–75% protamine lispro, 25% lispro	<0.25	1.5 h	Up to 10-16
70/30–70% protamine aspart, 30% aspart	<0.25	1.5 h	Up to 10-16
50/50–50% protamine lispro, 50% lispro	<0.25	1.5 h	Up to 10-16
70/30-70% NPH, 30% regular	0.5-1.0	Dual*	10-16
*Dual: two peaks-one at 2-3 h and the second one several hours later.			

Source: Harrison's Principles of Internal Medicine, 17th Edition (Eds. Fauci AS, Braunwald, E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalso J.), McGraw-Hill (2008)

Insulin regimens for the treatment of diabetes

- Conventional
- Intensified.
- Pump (with or without continuous glucose monitoring)

General daily dose of insulin:

- Type 1 DM: 0.5 - 1.0 U/kg divided into multiple doses
- Type 2 DM: 0.3 - 0.4 U/kg
- Intensive therapy can preserve endogenous insulin secretion

Intensified administration of insulin preserves endogenous insulin secretion and β-cell function.

Oral glucose-lowering therapies in T2DM

Insulin secretagogues

Sulfonylureas

- Agents: glibenclamide, glimepiride, glipizide, glipizide (extended release), glyburide (micronized)
- Advantages: lower fasting blood glucose
- Side effects: hypoglycemia weight gain, hyperinsulinemia
- Contraindications: renal/liver disease

Low price is the only advantage of sulfonylureas today. Since they can cause weight gain and protracted hypoglycaemia their importance decreases and are less used.

Nonsulfonylureas (meglitidines)

- Agents: repaglinide, nateglinide
- Advantages: short onset of action, lower postprandial glucose
- Side effects: hypoglycemia
- Contraindications: renal/liver disease

Incretin analogues

- Agents: exenatide, liraglutide
- Slow gastric emptying, Advantages: No hypoglycemia, appetite suppression, considerable weight reduction
- Disadvantages: Increased risk of thyroid C-cell tumors

DPP-4 inhibitors

- Agents: saxagliptin, sitagliptin, vidagliptin
- Conserve β-cell mass, promote insulin secretion in the absence of hypoglycemia or weight gain, preferential effect on postprandial blood glucose
- Disadvantages: Reduced dose in renal insufficiency
- Side effects: relatively few

Biguanides

- Agents: Metformin
- Mode of action:↓ Hepatic glucose production, weight loss, ↑ glucose utilization, ↓ insulin resistance
- Advantages: Weight loss, improved lipid profile, no hypoglycemia
- Disadvantages: lactic acidosis, diarrhea, nausea
- Contraindications: serum creatinine >1.5 mg/dL (men), >1.4 mg/dL (women), radiographic contrast studies, seriously ill patients, acidosis

α-glucosidase inhibitors

- Agents: acarbose, miglitol
- Mode of action: ↓ glucose absorption
- Advantages: No risk of hypoglycemia
- Side effects: GI flatulence, ↑ liver function tests
- Contraindications: renal/liver disease

Thiazolidinediones

- Agents: pioglitazone
- Mode of action: PPAR (peroxisome proliferator-activated receptor)-γ-agonism: ↓ insulin resistance, ↑ glucose utilization
- Advantages: ↓ Insulin and sulfonylurea requirements, ↓ triglycerides
- Side effects: Frequent hepatic monitoring for idiosyncratic hepatocellular injury
- Contraindications: liver disease, congestive heart failure

Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors

- Agents: empagliflozin, canagliflozin, dapagliflozin, ipragliflozin
- Action: blocks glucose reabsorption in the proximal renal tubule, leading to weight loss and A1C reduction in T2DM
- Side effects: urinary tract and urogenital infection

Amylin analogues

- Pramlimptine
- Action: delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety.
- Disadvantages: only in T1DM and for only adults

Guidelines for ongoing medical care for patients with DM

- Self-monitoring of blood glucose (individualized frequency)
- Hemoglobin A1C testing (2-4 times/year)
- Patient education in diabetes management (annual)
- Medical nutrition therapy and education (annual)
- Eye examination (annual)
- Foot examination (1–2 times/year by physician; daily by patient)
- Screening for diabetic nephropathy (microalbuminura test annually)
- Blood pressure measurement (quarterly)
- Lipid profile (annual)
- Influenza/pneumococcal immunizations

- Consider antiplatelet therapy

Complications of DM

Acute

- Diabetic ketoacidosis (DKA)
- Hyperglycemic hyperosmolar state (HHS)
- Lactate acidosis
- Hypoglycemia

Chronic

Macroangiopathy

- Accelerated atherosclerosis, esp. in coronary, cerebral, lower limb arteries

Microangiopathy

- Eye disease: Retinopathy (nonproliferative/proliferative), macular edema
- Nephropathy
- Neuropathy: Sensory and motor (mono-and polyneuropathy), autonomic

Other

- GI (gastroparesis, diarrhea)
- Genitourinary (uropathy/sexual dysfunction)
- Dermatologic
- Infectious
- Cataracts

Diabetic ketoacidosis

Symptoms

- Can occur as the first symptom of type 1 DM. Nausea/vomiting, thirst/polyuria, polydipsia, abdominal pain, shortness of breath

Physical findings

- Tachycardia, dry mucous membranes/reduced skin turgor, dehydration/hypotension, tachypnea/Kussmaul respiration, fruity odor, abdominal tenderness (may resemble acute, lethargy /obtundation/cerebral edema/possibly coma

Precipitating events

- Inadequate insulin administration, infection (pneumonia/urinary tract infection/gastroenteritis/sepsis), infarction (cerebral, coronary, mesenteric, peripheral), drugs (cocaine), pregnancy

The management of diabetic ketoacidosis

The management of DKA is not the competence of the General Practitioner. What he has to do is to:

1. Confirm diagnosis based on the history, clinical picture and, if possible, laboratory findings (elevated plasma glucose, positive serum ketones, metabolic acidosis). Laboratory

examination besides bedside glucose checking, however, should not cause any delay in the initiation of treatment: (saline infusion)
2. Arrange for urgent hospitalization at the emergency care unit.

At the emergency care unit:

1. Assess serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate), acid-base status - pH, HCO_3^-, pCO_2, renal function (creatinine, urine output)
2. Replace fluids: 2-3 L of 0.9% saline over first 1-3 h.
3. Administer regular insulin: IV (0.1 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase 2- to 10-fold if no response by 2-4 h. Be careful to hold potassium above 3.5 mmol/L!
4. Assess patient: What precipitated the episode (noncompliance, infection, trauma, infarction, cocaine)?
5. Administer intermediate or long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and subcutaneous insulin injection.

Hyperglycemic hyperosmolar state (HHS)

Clinical features

- Occurs typically in elderly individuals with T2DM. Several week history of polyuria, weight loss, and diminished oral intake. Mental confusion, lethargy, or coma. Profound dehydration and hyperosmolality, hypotension, tachycardia, altered mental status. Nausea, vomiting, and abdominal pain and the Kussmaul respirations are absent. Often precipitated by a serious, concurrent illness such as myocardial infarction or stroke, sepsis, pneumonia. In addition, a debilitating condition (prior stroke or dementia) or social situation that compromises water intake may contribute to the development of the disorder.

Treatment of hyperglycemic hyperosmolar state (HHS)

The management of HHS is not the competence of the General Practitioner. What he has to do is to:

1. Confirm diagnosis based on the history, clinical picture and, if possible, laboratory findings (elevated plasma glucose, sodium, BUN, no ketones and metabolic acidosis). Laboratory examination besides bedside glucose checking, however, should not cause any delay in the initiation of treatment: (saline infusion)
2. Arrange for urgent hospitalization at the emergency care unit.

At the emergency care unit:

- As with DKA, but: fluid replacement should initially stabilize the hemodynamic status of the patient. (1 to 3 L of 0.9% normal saline over the first 2 to 3 h). If the serum sodium is >150 mmol/L, 0.45% saline should be used. After hemodynamic stability is achieved use hypotonic fluids (0.45% saline IV) to reverse the free water deficit. IV insulin in bolus followed by a constant infusion rate

Chronic complications of diabetes mellitus

- Cardiovascular: 77%
- Renal: 9%
- Neurologic: 6%
- Ophthalmic: 4%

- Other: 4%

Glycemic control and complications 1. The DCCT (Diabetes Control and Complications Trial)

- >1400 individuals with type 1 DM
- Individuals in the intensive management group achieved a HbA1c 7.3% vs. conventional management group (9.1%). Improvement of glycemic control reduced nonproliferative and proliferative retinopathy by 47%, microalbuminuria by 39%, clinical nephropathy by 54%, and neuropathy by 60%

Glycemic control and complications 2: The UKPDS (United Kingdom Prospective Diabetes Study)

- >5000 individuals with type 2 DM
- Individuals in the intensive management group achieved a HbA1c 7.0% vs. conventional management group (7.9%). Improved glycemic control did not conclusively reduce cardiovascular mortality but was associated with improvement with lipoprotein risk profiles, such as reduced triglycerides and increased HDL. The beneficial effects of blood pressure control were greater than the beneficial effects of glycemic control. Lowering blood pressure to 144/82 mmHg reduced the risk of DM-related death, stroke, microvascular end points, retinopathy, and heart failure by 32-56%.

Ophthalmologic complications of DM

DM is the leading cause of blindness between 20-74 years. Duration of DM and degree of glycemic control are the best predictors of the development of retinopathy

Retinopathy: Appears late in the 1st decade or early in the 2nd decade of the disease. Found in all individuals who have had DM for >20 years. Forms:

- Non-proliferative (retinal vascular microaneurysms, blot hemorrhages, cotton wool spots, changes in venous vessel caliber, intraretinal microvascular abnormalities.)
- Proliferative: (retinal hypoxia → neovascularization. Appears near the optic nerve and/or macula and ruptures easily, → to vitreous hemorrhage, fibrosis, and ultimately retinal detachment.)

Macular oedema: detection by fluorescent angiography (FLAG)

Treatment:

- Prevention by intensive glycemic and blood pressure control (paradoxical worsening in the first 6-12 months of improved glycemic control)
- Laser photocoagulation

Renal complications of DM

Diabetic nephropathy is the leading cause of end stage renal disease. Retinopathy is almost always present. Smoking accelerates the decline in renal function.

Pathomechanism: chronic hyperglycemia, soluble factors: growth factors, AT II, endothelin, AGEs, hemodynamic alterations in the renal microcirculation, structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis). Some of these effects may be mediated through AT-II receptors.

Treatment of diabetic nephropathy

Prevention is the most important. Early nephrology consultation is indicated. Interventions:

1) Near normalization of glycemia. Insulin requirement may fall. Sulfonylureas and metformin are contraindicated in advanced renal insufficiency.
2) Strict blood pressure control. Target values:
   - without proteinuria: <130/80 mmHg
   - microalbuminuria or overt nephropathy: 125/75 mmHg
3) Administration of ACE inhibitors or ARBs. If unfeasible, Ca-channel blockers (non-dihydropyridines)
4) Treatment of dyslipidemia
5) Restriction of protein intake:
   - with microalbuminuria: 0.8 g/kg
   - overt nephropathy: <0.8 g/kg
6) Dialysis, renal (or pancreas-kidney) transplantation

Diabetic neuropathy

Occurs in 50% of individuals with long-standing DM. Forms:

Polyneuropathy

- Distal symmetric polyneuropathy, polyradiculopathy), mononeuropathy: sensory loss, hyperesthesia, paresthesia, dysesthesia, sensation of numbness, tingling, sharpness, or severe burning pain, pain and motor weakness in the distribution of a single nerve

Autonomic neuropathy

- Cardiovascular system: resting tachycardia on Holter and ABPM, orthostatic hypotension, non-dipper hypertension, sudden death
- Gastroparesis and bladder-emptying abnormalities
- Hyperhidrosis of the upper and anhydrosis of the lower extremities: dry skin with cracking, which increases the risk of foot ulcers.
  - Reduction of counterregulatory hormone release: hypoglycemia unawareness
- Examination: sensory loss, loss of ankle reflexes, and abnormal position sense
- 128 Hz tuning fork, monofilament (5.07, 10-g monofilament)

Treatment of diabetic neuropathy

Only symptomatic treatment is available. Improved glycemic control. Avoidance of neurotoxins (alcohol). Supplementation with vitamins (B12, B6, folate). Prevention of ulcers. Temporary use of analgesics.

- Chronic, painful diabetic neuropathy: tricyclic antidepressants (amitriptyline, desipramine, nortriptyline), gabapentin, NSAIDs, and other agents (mexilitine, phenytoin, carbamazepine, capsaicin cream).
- Referral to a pain management center may be necessary.
- Therapy of orthostatic hypotension: adequate salt intake, avoidance of dehydration and diuretics, and lower extremity support hose.

Gastrointestinal dysfunction

- Gastroparesis
- Altered small- and large-bowel motility

Genitourinary dysfunction

- Cystopathy
- Erectile dysfunction and retrograde ejaculation
- Female sexual dysfunction

Cardiovascular disease risk in diabetes

- Individuals diagnosed with diabetes should be considered as patients who have already had diabetes, because the long-term mortality of patients with diabetes and without myocardial infarction is the same of those with myocardial infarction and without diabetes.
- Evidence of atherosclerotic vascular disease should be sought in an individual with diabetes.
- The absence of chest pain ("silent ischemia") is common in individuals with diabetes.
- The increase in cardiovascular morbidity and mortality appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors. For example, after controlling for all known cardiovascular risk factors, T2DM increases the cardiovascular death rate 2-fold in men and 4-fold in women.
- Additional risk factors specific to the diabetic population include microalbuminuria, gross proteinuria, an elevation of serum creatinine, and abnormal platelet function.
- Insulin resistance results in increased thrombosis and decreased fibrinolysis
- Cerebrovascular disease is increased, 3-fold increase in stroke).
- Incidence of congestive heart failure (diabetic cardiomyopathy). Multifactorial etiology: myocardial ischemia from atherosclerosis, hypertension, and myocardial cell dysfunction secondary to chronic hyperglycemia.

Therapy

- Antihypertensive agents: ACE inhibitors, ARB-s, β-blockers (carvedilol, nebivolol)
- Treatment of dyslipidemia. DM itself does not increase levels of LDL, but the small dense LDL particles found in T2DM are more atherogenic because they are more easily glycated and susceptible to oxidation. Cholesterol-lowering therapy prolongs the survival of diabetics with known coronary disease. Target lipid values in diabetic individuals without cardiovascular disease:
    - LDL <1.8 mmol/L
    - HDL >1.1 mmol/L (40 mg/dL) in men and >1.38 mmol/L (50 mg/dL) in women
    - triglycerides <1.7 mmol/L (150 mg/dL). This is the order of priorities in the treatment
- Drugs: statins (simvastatin, atorvastatin, rosuvastatin), with combination of ezetimibe, if necessary), fibrates (fenofibrate)
- Antiplatelet therapy: aspirin 81 to 325 mg/d. Antiplatelet agents have not been effective in the primary prevention of cardiovascular disease events in diabetes but should be given for secondary prevention.

Lower extremity complications

DM is the leading cause of nontraumatic lower extremity amputation. Approx. 15% of individuals with DM develop a foot ulcer and 14 to 24% risk with that ulcer or subsequent ulceration will have amputation. The reasons for the increased incidence: neuropathy, abnormal foot biomechanics, peripheral arterial disease, and poor wound healing. The optimal therapy is prevention.

Diabetic ulcers of the lower extremity

Origin: primarily neuropathic (no accompanying infection) and cellulitis w/wo osteomyelitis. Diagnosis: bacterial cultures, plain radiographs, nuclear medicine bone scans, In-labeled white cell studies, MRI, bone biopsy and culture.

Therapy: off-loading: bed rest, contact casting, etc., debridement, wound dressings, appropriate use of antibiotics (cephalosporin, clindamycin, amoxicillin/clavulanate, fluoroquinolones), cefotetan, vancomycin), revascularization, limited amputation

Education of the patient with diabetic foot

1) Careful selection of footwear
2) Daily inspection of the feet to detect early signs of poor-fitting footwear or minor trauma
3) Daily foot hygiene to keep the skin clean and moist
4) Avoidance of self-treatment of foot abnormalities and high-risk behavior (e.g., walking barefoot)
5) Prompt consultation with a health care provider if an abnormality arises.
6) Evaluation by a foot care specialist: orthotic shoes and devices, callus management, nail care, and prophylactic measures to reduce increased skin pressure from abnormal bony architecture.

Infections in DM

Greater frequency and severity of infection. Reasons: abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia and diminished vascularization.

Infectious agents:

- Candida, Torulopsis glabrata and other fungal species
- rhinocerebral mucormycosis
- emphysematous infections of the gallbladder and urinary tract
- “malignant” or invasive otitis externa (usually secondary to P. aeruginosa)
- gram-negative organisms, S. aureus, and Mycobacterium tuberculosis, Escherichia coli,
- Pneumonia, urinary tract, and skin and soft tissue infections (furunculosis), vulvovaginitis
- Periodontal disease, early loss of teeth

Dermatologic manifestations of DM

- Protracted wound healing and skin ulcerations are the most common.
- Rubeosis diabetica on the face
- Diabetic dermopathy
- Necrobiosis lipoidica
- Xerosis and pruritus are common and are relieved by skin moisturizers

The prevention of T2DM

- Intensive changes in lifestyle (diet and exercise for 30 min/day five times/week): 58%
- Metformin: 31%
- Individuals with a strong family history, those at high risk for developing DM, or those with IFG or IGT should be strongly encouraged to maintain a normal body mass index (BMI) and engage in regular physical activity!

References

Harrison's Principles of Internal Medicine, 20 th ed. (Eds. Kasper DL, Fauci AS, Hauser S, et al.) McGraw-Hill (2018)

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Emergency in Primary Care

Krisztián Vörös MD, PhD

Meeting emergency

Appr. 8 ”real” emergency/year;

22 cardiac arrests, 10 deaths in 1650 Swiss practices/5years

Office emergency

- Misinterpret the urgency of their condition
- Purposefully avoid the emergency department
- Parents unaware of the severity of their child’s illness
- Patients value and prefer primary care

Table 2. Adjusted Mean Satisfaction Score for Care for Most Recent Urgent Health Problem Among 1,227 Patients Who Used Different Services

Site of Service*	Adjusted Score† Mean (SE)	95% CI
Family physician‡	6.1 (0.14)	5.8-6.4
After-hours clinic§	5.6 (0.20)	5.2-6.0
Emergency department¶	5.3 (0.08)	5.2-5.5
Telephone health advisory service	4.8 (0.32)	4.2-5.5
Walk-in clinic	4.7 (0.21)	4.3-5.1
More than 1 service	4.7 (0.17)	4.4-5.0

ED attendances rising

Inappropriate: 20-40%, paediatric visits: 58-82%

Consequences

- overcrowding, long waiting times
- increased number of hospital admissions
- work overload for ED stuff
- costs

Causes

- Perceived severity of condition
- Patient variables: young, female, low income
- Psychosocial factors: family conflicts, ill relative, financial problems, substance abuse…
- Frequent users have psychiatric co-morbidity
    - 93%
    - patients don’t present with psychosocial complaints
    - doctors don’t recognize it
    - not identified, not followed up by psychiatrists
- Efficiency of ED
    - psychiatric diagnosis 9%

Problems with primary care

- Incomplete awareness of out-of-hours GP service
- Patients lacking a usual source of care, regular physician
- Difficulties in accessing primary care
- Advice by PCP to utilize ED
- Communication problems (unhelpful staff at PCP)
- Dissatisfaction with PCP

Solutions

- Patient education - what conditions can be cared for in PCP office
- More availability of office appointments
- Good communication, patient-doctor relationship
- Quick recovery after ED visit - strongest correlation: having a PCP

Meeting emergency

- Small villages
- Urgent care centres
- During surgery hours
- During outdoor visits
- As a neighbour, passer-by, etc.
- Relatively common
- Important to recognize, not always evident
- Prehospital care can be crucial
- Difficulties, obstacles
- Lack of equipment (defibrillator, infusion pump, endotracheal intubation)

Lack of staff

- Alone
- Practice nurse
- Colleague

Lack of experience

- Small number of emergencies

Proximity of hospital – easy to shift off emergencies

Solutions

- Proper planning
- Acquisition of emergency supplies
- In experienced hands - regular training - maintaining skills
- Create written emergency protocol
- Practice for emergencies

Giving advice

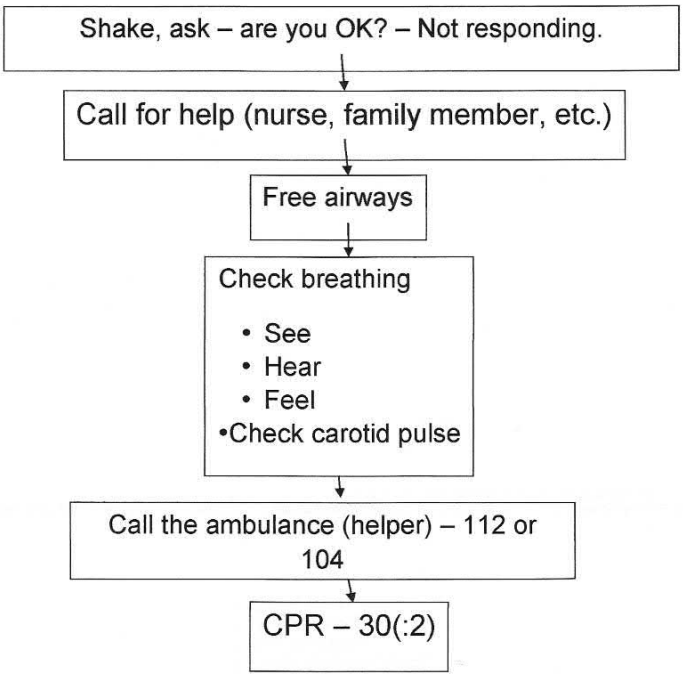
- Find out if you or your family are at risk
- Talk to your doctor about what you should do if an emergency happens
- Know when your doctor's office is open and how to contact your doctor when the office is closed

- Find out which emergency room or urgent care centre you should go to in an emergency
- Know how to call an ambulance, help
- Keep a list of the medicines you take and your medical problems
- Learn basic first aid skills

Most common emergencies

- Cardiac emergencies
- Asthma exacerbation
- Psychiatric
- Impaired consciousness
- Hypoglycaemia
- Anaphylaxis
- Seizure
- Shock
- Poisoning / Drug overdose

Basic life support (BLS)

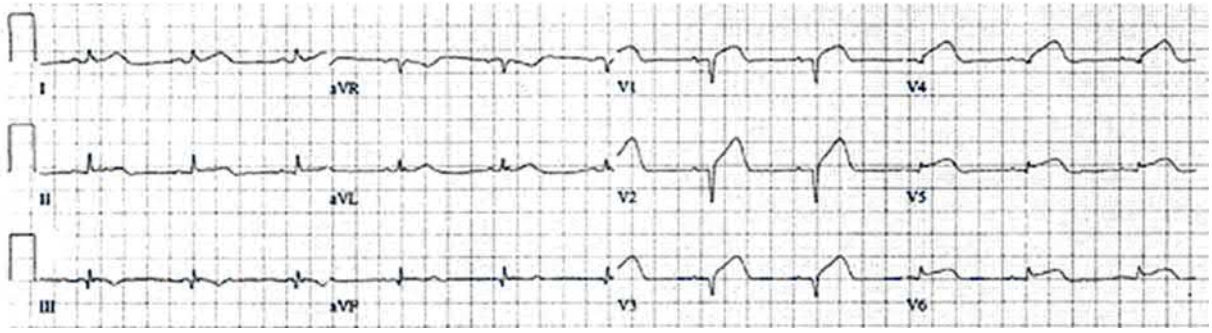


Clinical case 1.

74 year-old woman, history: diabetes, hypertension, hyperlipidaemia

Call: Strong chest pain on the left side, weakness, dyspnoea

Physical: BP: 120/70 mmHg, P: 75/min, rales, epigastrial tenderness, no arrhythmia



Acute extensive anterior STEMI, with heart failure.

Therapy: aspirin po. 500 mg, clopidogrel 600 mg, nitroglycerine spray, iv. access, furosemide 60 mg, morphine titrated (5 mg)

Ambulance → PCI centre

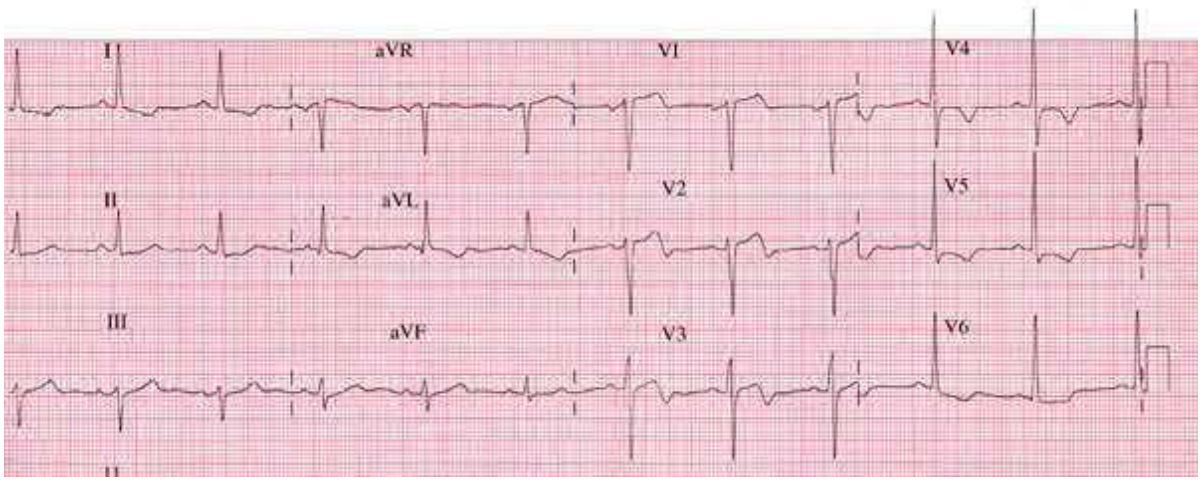
NB: high risk, typical symptoms, typical ECG

Clinical case 2.

71 year-old woman, smoker, history: hypertension, hyperlipidaemia, hypothyroidism + compliance problems. chemotherapy - lung cancer

Nausea during the night, moderate chest pain

Physical: nothing significant



Unstable angina

Treatment: aspirin 500 mg po., clopidogrel 300 mg po., metoprolol 25 mg po., iv. access

Ambulance, ICU

Cause: anaemia following chemotherapy

Cardiovascular emergencies

Acute coronary syndrome

Myocardial ischemia, due to an imbalance between supply and demand of myocardial oxygen.

Risk factors: hypertension, diabetes, smoking, cholesterol, family history, age, sex, prior CVD.

History (chest pressure or heaviness, neck, jaw, ear, arm, or epigastric discomfort, shortness of breath, weakness, nausea – DM!, anxiety, diaphoresis)

Physical: check for pulmonary oedema, arrhythmia, (new) murmurs, hyper- hypotension

ECG:

- (Transient) ST segment elevations
- Dynamic T-wave changes, either inversions, normalizations
- ST depression (junctional, downsloping, or horizontal)
- Normal or unchanged ECG does not exclude ACS
- STEMI (3 hours - 60min., 12 hours - 90min.) - PCI
- NSTEMI, unstable angina - cardiology, intensive care unit

Prehospital care

- Aspirin (500 mg), clopidogrel 300-600 mg, (heparin – 5000 U bolus, LMWH)
- Nitroglycerin (sublingual, transdermal, infusion)
- Oxygen
- Morphine 5-10 mg iv. - titrate to pain
- Obtain IV access
- Perform pulsoximetry

Clinical case 1.

- 30 year-old man, BMI: 40.4 kg/m2
- History: treated hypertension, stopped taking his medication
- Current history: pulsating headache, high blood pressure
- Physical: BP: 205/118 mmHg 80/min, otherwise normal, ECG normal
- Treatment: captopril 25mg orally, repeated; metamizole 1000 mg orally
- Restart past medications (lisinopril, amlodipine, bisoprolol)

Clinical case 2.

- 63 year-old man with known hypertension
- Stopped his medication months ago
- History: claims to be well
- Physical: nothing notable, but BP: 195/110 mmHg, P: 85/min
- Acute treatment: none
- Restart previous medications (metoprolol retard, felodipine)

Clinical case 3.

- 78 year-old woman
- Stumbled 2 hours ago
- Lies on the floor, severe pain in her left hip
- Physical: BP: 195/110, unable to elevate affected leg, no other injuries, extremity slightly shortened, abducted, and externally rotated
- Treatment: iv. access, tramadol 50 mg iv., transfer to hospital on vacuum mattress
- Control BP after tramadol: 160/90 mmHg

Hypertensive emergencies

Hypertensive emergency (crisis)

- Severe hypertension with acute impairment of an organ system (CNS, CV, renal).
- Hypertensive urgency. BP is a potential risk, with no acute end-organ damage
- Main risk factor for a crisis/urgency: Insufficient blood pressure control

History

- Medications (hypertensive medications and compliance, drugs)
- Other medical problems (hypertension, thyroid disease, Cushing disease, renal disease)

Complications

- CNS: headaches, blurred vision, nausea, weakness, confusion, focal neurologic findings, dizziness, ataxia
- CV: heart failure, angina, dissecting aneurysm
- Renal manifestations: hematuria, oliguria

Causes

- ineffective medications (lack of regular BP check)
- bad compliance
- anxiety, panic attack
- pain
- other (renal failure, eclampsia, head injuries, pheochromocytoma, drugs)
- unexplained

Treatment

- Treat the cause if possible (pain, anxiety)
- Regular drugs not taken - rapid-acting drug, give back regular drug
- Regular drugs not enough - rapid-acting drug, start new medication, continue the previous
- Rapid BP lowering usually not necessary, normal blood-pressure to be reached within days/weeks
- Acute impairment of on organ system might need more aggressive treatment

Treatment – drugs

- captopril 25 mg po.
- uradipil 12,5-25-50 mg. iv.
- nitroglycerine spray (HF, ischemia)
- furosemide 20-40 (or more) mg iv. (HF, renal failure)
- metoprolol 50 mg po., 3-5 mg iv. (ischemia, arrhythmia)
- verapamil 5 mg iv. (arrhythmia)
- nifedipine spray (not recommended, with β-blocker)

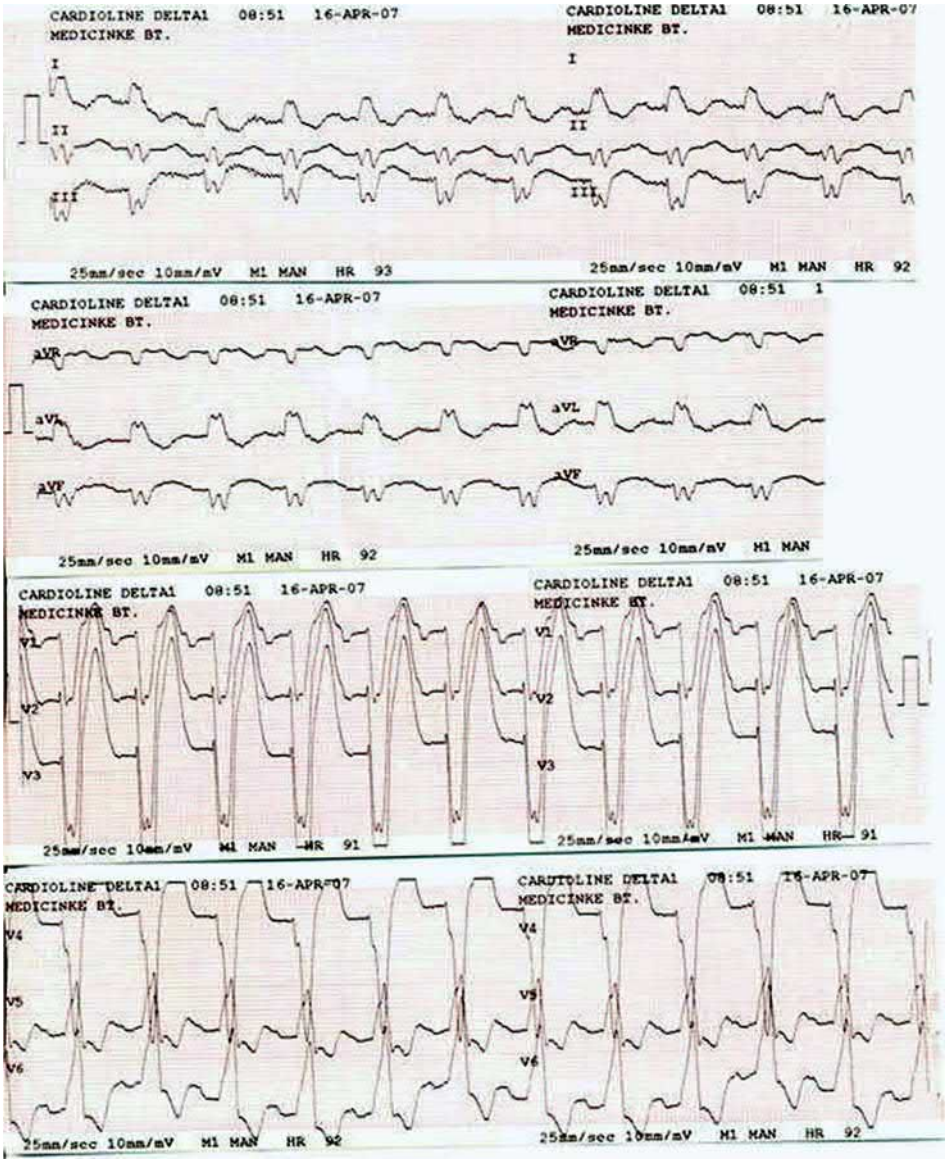
Treatment – indications of rapid BP lowering

- Acute myocardial ischemia (nitroglycerin, β-blockers, angiotensin-converting enzyme inhibitors - usually iv.)
- CHF with pulmonary edema (nitroglycerin, furosemid, morphine iv., captopril po.)
- Hypertensive encephalopathy (nimodipine, nicardipine, verapamil iv.)

Follow-up

Clinical case 1.

- 59 year-old man, history: alcohol abuse, hypertension - not treated
- History: dyspnea in rest and during the night, unable to lie
- Physical: tachycardia, BP: 145/80 mmHg, P: 95/min, rales, no edema



- ECG: sinus tachycardia, I. AV block, LBBB
- Acute left-sided heart failure
- Hospital: dilatative cardiomyopathy (alcoholic)
  ECHO: diffuse hypokinesis, EF: 25%
- Treatment: furosemide iv. 80 mg, transdermal nitroglycerin, oxygen in ambulance
- Long term treatment: ramipril, bisoprolol, furosemide, spironolactone

Clinical case 2.

- History: man, 64 y, not followed-up
- Complains of abdominal pain after drinking milk, since then severe dyspnea, almost unable to walk

- Physical: edema, rales, dullness, BP: 145/80 mmHg, P: 85/min, aortic murmur
- ECG: flat T waves in every lead
- Treatment: furosemide, nitroglycerin
- Diagnosis: acute heart failure
- ECHO: severe aortic stenosis - surgery?

Heart failure – pulmonary edema

Most common acute causes

- Ischemic (or other origin) myocardial malfunction
- Severe hypertension
- Arrhythmias (AF with rapid ventricular rate, VT)
- Structural heart or valve diseases
- Myocarditis, pericarditis
- Physical stress
- Other: infection, PE, noncompliance with medical therapy, hyperthyroidism

History

- Dyspnea (exertion, in rest, paroxysmal nocturnal)
- Cough productive of pink, frothy sputum
- Oedema (legs, hip)
- Weakness
- Other diseases (CMP, valvular heart disease, alcohol use, hypertension, IHD)

Physical

- Peripheral oedema, jugular venous distention, and tachycardia – most sensitive
- Orthopnea, tachypnea
- Hypertension
- Pulsus alternans (Regular alternation of the force of the arterial pulse. It almost invariably indicates the presence of severe left ventricular systolic dysfunction. Not every heart muscle cell contracts at every beat. Diastolic volume is changed.)
- Skin - diaphoretic or cold, grey, cyanotic
- Wheezing or rales, effusion
- Apical impulse displaced laterally
- Cardiac auscultation S3 or S4.

Treatment

- Reduce venous return (elevate the head of the bed, patient in sitting position, legs dangling
- Obtain iv. access, administer oxygen
- Medications: see next slide
- Consider treatable cause (arrhythmia: lidocain, metoprolol, atropine), fever, severe hypertension (ACEI, BB), ischemia, bronchospasm: albuterol)
- Intubation, facemask - PEEP valve

Treatment - drugs

- Nitroglycerine spray - 1 spray every 5-10 min, max. 3 times, transdermal patch - check BP

- Furosemide iv. 40-80 mg
- Morphine 5-10 mg - decrease ineffective hyperventilation, sympathicotonia
- Nitroglycerine - 5 mg into 500 ml infusion, 10-20 drops/min.=5-10 µg/min
- Dopamine - 50 mg into infusion, 60 drops/min

Clinical case 1.

- 50 year-old man, bus driver, BMI: 31.4 kg/m^2
- History: joint gout, sinus tachycardia
- Current: pain and tenderness of right leg, calf muscle
- Physical: minimal oedema
- Obvious cause: erroneous pedals
- Ultrasonography: normal

Clinical case 2.

- 45 year-old man, obese, history of diabetes, erysipelas???
- Oedema of leg for 4 days, no pain, no fever
- Swollen leg, no pain on dorsiflexion
- History: 1984 – thrombophlebitis, 1989 – trauma of leg, followed by thrombophlebitis
- Ultrasonography, d-dimer: DVT
- No thrombophilia, tumour

Deep Venous Thrombosis (DVT)

Bedside diagnosis of venous thrombosis is insensitive and inaccurate (little obstruction, rapidly developed collaterals, minimal inflammation)

History/Physical:

- Rapid development of unilateral oedema
- Leg pain on dorsiflexion (Homans sign)
- Tenderness (calf muscle, course of the deep veins)
- Warmth and erythema
- Swelling, collateral superficial veins

Risk factors (sensitive)

- Age
- Immobilization (pregnancy, surgery, trips)
- Diseases (DVT, cancer, stroke, AMI, CHF, nephrosis, CU, SLE)
- Trauma, fractures
- Hematologic diseases (PV, thrombocytosis, coagulation disorder)
- IV. drug abuse, contraceptives

Treatment

- Transfer to hospital
- Patient should not walk (ambulance transfer)
- LMWH, heparin
- Compression stockings

Diagnosis

- D-dimer + ultrasonography

Follow-up

- Rule out malignancies, thrombophilias

Pulmonary embolism – DVT

History

- Pain (chest, back, shoulder, respiratophasic or pleuritic – youngsters!)
- Dyspnea, hemoptosis, cough, hiccough
- Syncope
- Fever
- Pneumonia – not improving after treatment
- DVT

Physical

- Many patients have atypical or no symptoms
- Chest wall tenderness
- Wheezing, pulmonary rub, rales
- Arrhythmia (atrial), tachycardia
- Hypotension in massive PE (acute cor pulmonale)
- Accentuated second heart sound, gallop rhythm
- Diaphoresis, cyanosis, signs of DVT

ECG

- tachycardia and nonspecific ST-T abnormalities
- right heart strain (P-pulm, right dev, RBBB, SI-QIII-TIII, AF)

Acute bronchial asthma, COPD exacerbation

Causes

- Infection
- Allergens (pets, pollen, aspirin, food)
- Exercise
- Air pollution

History

- Severity (medicines taken, hospitalization)
- Duration of symptoms
- Degree of dyspnea
- Medicine compliance

Physical

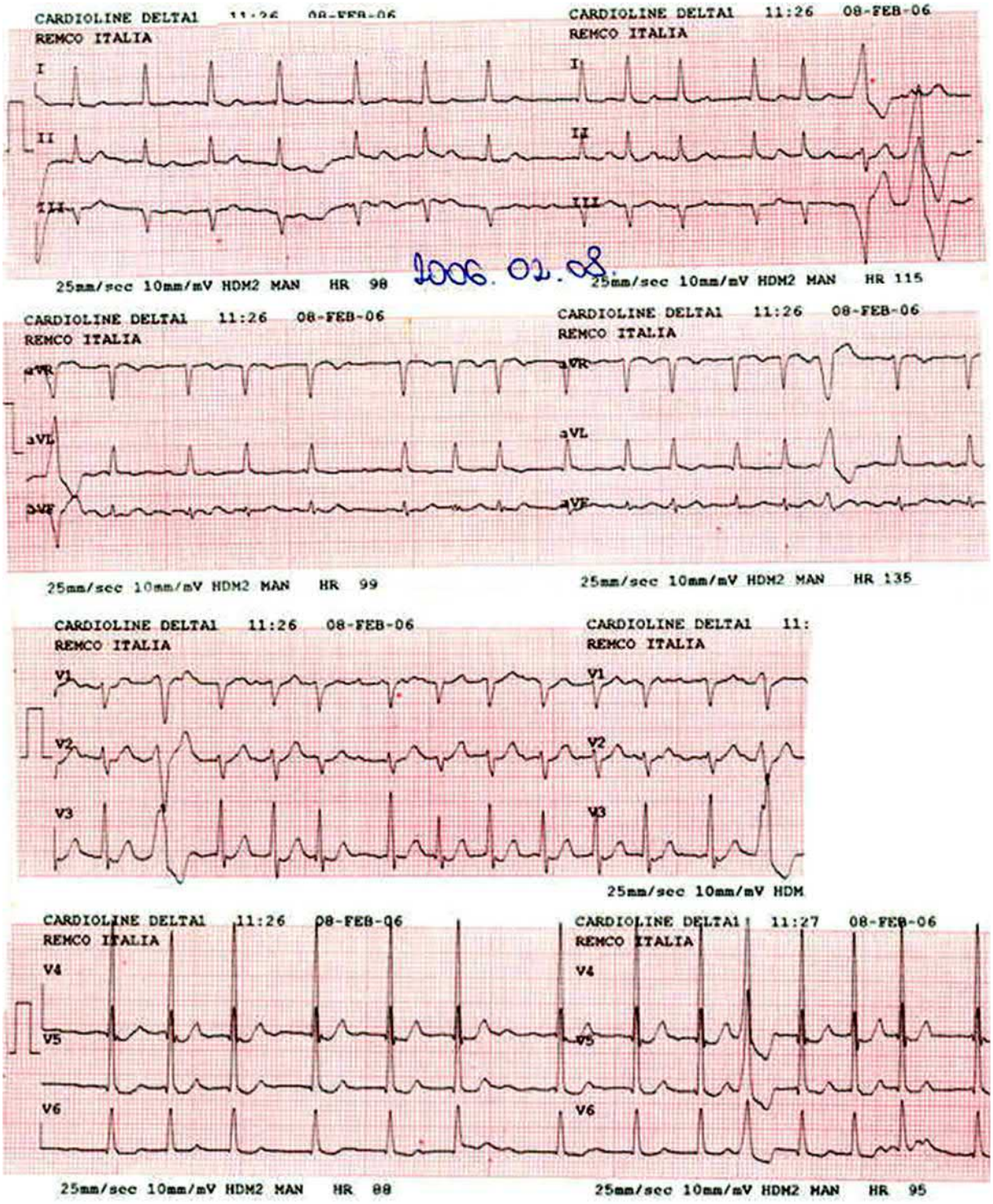
- Ability to speak
- Level of alertness
- Stridor, wheezing, inspiration-expiration ratio
- Tachycardia, tachypnoe
- Accessory muscle use, nasal flaring
- Ability to lie < sitting position < hunched-over sitting position (tripod position)
- Diaphoresis
- Cyanosis

Treatment

- Oxygen, if available
- Beta-adrenergic agents in nebulizer (salbutamol, albuterol spray)
- Ipratropium (smokers, COPD)
- Methylprednisolone 80-125 mg iv.
- Theophylline max. 3 mg/kg iv.
- Terbutaline 0.25 mg sc., Epinephrine 0.3-0.5 mg sc. (in infusion 20 drop/min)
- Obtain iv. access if necessary

Clinical case 1.

- 73 year-old man, history: hypertension, arthrosis, hyperlipidemia
- Previous year: lab tests – normal, ABPM: controlled hypertension (112/62-69), ECG: sinus rhythm, left R axis, QRS: 100 ms, normal repolarisation
- Current history: swollen, painful knee
- Physical: arrhythmia, 145/82 mmHg

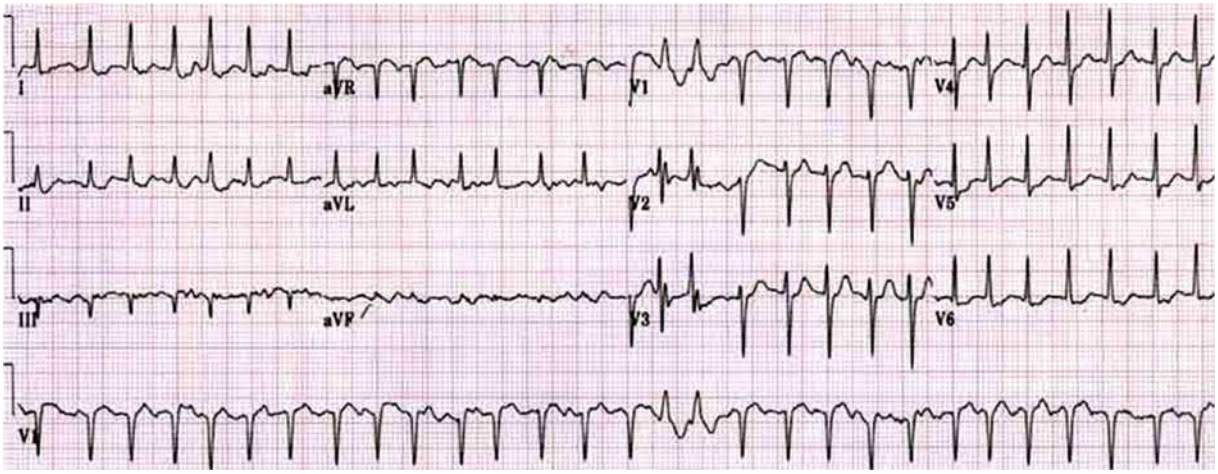


- Diagnosis: paroxysmal atrial fibrillation for unknown period of time
- Treatment: bisoprolol to therapy (perindopril, hydrochlorothiazide), warfarin
- Regular control visits: heart rate, INR, heart failure
- ECHO: concentric ventricular hypertrophy, EF:50%, atrial and ventricular dilatation
- Rate control since then

Clinical case 2.

- 71 year-old woman, history: COPD (smoker)

- Viral infection, increased medication doses of theophylline, formeterol, fenoterol+ipratropium
- Complains of weakness, palpitation
- Physical: BP: 100/70 mmHg P: 170/min



- Treatment: 5 mg verapamil iv.
- Transfer to hospital
- Sinus rhythm returned spontaneously after reviewing medication
- ECHO: normal findings
- Anticoagulation and bisoprolol started
- 3 months in sinus rhythm, Holter-monitoring
- Anticoagulation stopped

Atrial fibrillation

History

- Palpitations
- Fatigue or poor exercise tolerance
- Dyspnea
- Chest pain (true angina)
- Syncope

Physical

- Irregular pulse, with or without tachycardia
- Hypotension and poor perfusion
- Signs of embolization (TIA, stroke, peripheral arterial embolization)
- Signs of congestive heart failure (rales, oedema, gallop)

ECG

- irregular QRS complexes, no P wave (inferior, V1-2)

Causes

Acute diseases	Chronic diseases
• AMI, Pericarditis, PE • Cardiothoracic surgery • Holiday heart, illegal drugs (cocaine, amphetamine) • Lone fibrillation (no structural heart disease)	• Valvular diseases • Hypertension • Structural heart diseases, IHD

Treatment

Rate control (if necessary):

- beta-blockers: metoprolol 5-10 mg iv. (thyrotoxicosis, AMI, sympathycotony)
- verapamil or diltiazem: 2,5-5 mg/10-20 mg iv.
- digoxin: 0,5 mg iv. - in CHF, controversial: acts slowly, can increase duration of paroxysmal AF, do not prevent rapid ventricular rate

Clinical case 1.

- 26 year-old man, history: nothing remarkable
- 10 days ago sore throat, mild fever for 2 days
- Got better a week ago, throat still feels dry, „itching”
- Weakness, lost 8 kg-s of his weight during a week
- Thirsty all the time, drinks much, urinates often
- Blood sugar level: 24 mmol/L
- Treatment: iv. fluid replacement, transfer to hospital
- Diagnosis: Type 1 diabetes mellitus

Clinical case 2.

- The same young man
- 4 hours ago started vomiting, shivers, cold sweat, looks anxious
- Blood sugar level: Low
- No appetite, eat less for breakfast and lunch
- Treatment: glucosum 40% - 50 ml, 50 ml in 500 ml saline, transfer to hospital
- Diagnosis: hypoglycemia, acute viral gastritis
- Got better quickly

Hypoglycemia

Glucose level at which an individual becomes symptomatic (<2.0 mmol/L - variable)

History

- DM – insulin, oral hypoglycemic agent
- alcoholism, hepatic failure, starvation

Physical

- CNS: headache, confusion, focal neur. findings
- Adrenergic symptoms: sweating, anxiety, tremulousness, nervousness, palpitation
- GI symptoms: hunger, nausea

Causes

- Exercise
- Medication overdose, change
- Diet change
- Infections

Treatment

- Administer Glucosum 40%, 50-100 ml
- Glucagon 1mg im. iv. sc.
- Drinking/Eating

Hyperglycemia, DKA (Diabetic ketoacidosis)

Absolute or relative insulin deficiency cause: hyperglycemia, dehydration, and acidosis. Most common causes: infection (UTI), disruption of insulin treatment, new onset of diabetes, serious disease (AMI, stroke, trauma).

History/Physical

- Thirst, polyuria, polydipsia, weight-loss, weakness, fatigue, confusion, abdominal pain
- Ill appearance, dry skin, mucous membranes, decreased skin turgor, tachycardia, hypotension, tachypnoea, ketotic breath

Treatment

- Isotonic saline solution up to 1 L (+ insulin), hospitalization

Clinical case 1.

- 20 year-old woman, with history of asthma
- Strong abdominal pain this night, nausea, vomiting
- No dysuria, normal frequency, had normal stool in the evening
- Got better, no nausea, still moderate flank pain on the right side
- Physical: flank tenderness, dipstick: blood positive
- Diagnosis: acute nephrolithiasis
- Treatment: diclofenac 2x75 mg orally, drotaverin
- Renal RTG: technical error US: 2 calix stones
- Referral to an urologist

Clinical case 2.

- 45 year-old man, history: nothing remarkable, known renal calculi
- Excruciating pain, radiating from the flank to lower abdomen on the left side
- Crawling on the floor, wife and three children watching frightened, astonished
- Took some oral pain killers (?)
- Diagnosis: acute nephrolithiasis
- Treatment: obtain iv. access, morphine iv. (to achieve quick effect), hospitalization

Acute nephrolithiasis

History

- Known renal calculi
- Mild or severe deep flank pain - kidney

- Unrelenting, excruciating pain, radiating from the flank to lower abdomen and testicles or labia on the affected side - ureter
- Urinary frequency and dysuria - ureter, urinary bladder
- Intense nausea
- Unable to lie still

Physical

- Gross haematuria
- Flank tenderness (ipsilateral)
- Tenderness on the affected side
- Palpable kidney
- Bowel sounds may be hypoactive

Treatment

- 20% of patients require hospital admission because of unrelenting pain, inability to retain enteral fluids, proximal urinary tract infection (UTI), or inability to pass the stone
- Analgesic: diclofenac (75mg) im., iv. metamizole (1-2 g), tramadol (50-100 mg), pethidine (25-50 mg), morphine 5-10 mg
- Smooth muscle relaxants: drotaverine 80 mg, nitroglycerine, nifedipine orally or spray
- Antiemetics: vitamin B6 - 50 mg, metoclopamide 10 mg

Cholecystitis and biliary colic

When gallstones temporarily obstruct the cystic duct or pass through into the common bile duct, gallstones become symptomatic and biliary colic develops. When the cystic duct or common bile duct becomes obstructed for hours or gallstones irritate the gallbladder, cholecystitis develops. Choledocholithiasis occurs when the stones become lodged in the common bile duct, resulting in possible cholangitis and ascending infections. 10-20% of adults have gallstones, 1-3% of them develop symptoms of gallstones. Major risk factors: gender, obesity, age. Complicated cholecystitis has 25% mortality (gangrene, empyema, perforation of gallbladder).

History

- 1-5 hours of severe, constant (not colicky) pain, in the epigastrium or right upper quadrant, may radiate to the right scapular region or back
- Develops hours after a meal (large, fatty), occurs frequently at night
- Nausea, vomiting, pleuritic pain
- Persistent pain (hours-days), vomiting, fever - cholecystitis

Physical

- Patients with gallbladder colic have relatively normal vital signs
- Epigastric or right upper quadrant tenderness
- Bloating
- Guarding or fullness in the right upper quadrant on palpation
- Peritoneal signs!
- Jaundice is rare
- Hydrops vesicae fellae

Treatment

- Cholecystitis, peritoneal signs, jaundice, fever, persistent pain usually means hospitalization

- Diet
- Antispasmodics: drotaverine (80 mg)
- Analgesics: metamizole (1-2 g), pethidine (meperidine 25-75 mg)
- Antiemetics: Vitmaine B6 50 mg, metoclopamide 10 mg, thiethylperazine 0,5-1 g

Clinical case

- Man, aged 59, complains of deep epigastric pain for 4 days, fever for 3 days, lack of appetite, sweating when eating
- Normal stool (less in volume, because hardly eats), urine
- History: gallstones
- Physical: epigastric rigidity, mild tenderness in the right, medium tenderness in the epigastric and left upper quadrant, normal vital signs, 104/71 -100, jaundice
- Treatment: drotaverin, metamizol iv.
- Transfer to hospitals – Pancreatitis?
- Lab test: GOT:81 U/l, GPT:73 U/l, GGT:124 U/l, Alc. Phos:403 U/l, Bilirubin:89 umol/l, Amylase:1491 U/l, WBC:14.8 G/l, CRP:248.52 mg/l, We:56 mm/h
- US: overlying gas shadows, cholelithiasis, choledocholithiasis
- Final diagnosis: mild acute pancreatitis, caused biliary stones
- Referred for cholecystectomy later

Acute pancreatitis

- Inflammatory process in which pancreatic enzymes autodigest the gland
- Mild 80%, severe 20% of presentations
- History: epigastric pain radiating to the back, nausea and/or vomiting
- Phycisal: abdominal tenderness, distension, guarding, and rigidity, mild jaundice, diminished bowel sounds, fever, tachycardia, tachypnea, hypotension

Causes

- Long-standing and / or binge alcohol consumption
- Biliary stone disease
- Rare causes: medications, ERCP, hypertriglyceridemia, peptic ulcer, trauma, infections, cancer

Workup

- Lab tests, US, CT, plain radiography

Acute treatment

- Analgesics (metamizol, pethidine), spasmolytics (drotaverine), iv. access

Clinical case

- 31 year-old man, history: nothing remarkable
- Repeating episodes of low back pain, URTI
- Strong pain in stomach, weight loss for month
- Physical: epigastrial tenderness, anxiety, depressed mood, carcinophobia
- Lab test: normal, US: normal, Endoscopy: gastritis, reflux disease
- Accepted gastroenterological follow-up, he and his wife rejects referral to psychiatrist
- Keeps losing weight, pain worsens, control at gastroenterologist: recommends hospitalization for evaluating for Addison, tumour (weight loss, weakness)

- During control visit suddenly palpitation, chest pain, collapsing
- Diagnosis: depression, panic attack, somatization
- Background: family conflicts in childhood, personality traits
- Treatment: ambulatory psychiatric follow-up, hospitalization, antidepressants, anxiolytics

Depression and suicide

- Depression is a potentially life-threatening mood disorder
- Ninth leading reported cause of death, third in youngsters
- More men than women die from suicide by a factor of 4.5:1, extremely high rates over age 85
- 8-25 attempted suicides occur for every completion, these are mainly expressions of extreme distress
- Risk factors: history of mental problems or substance abuse, suicide, family violence, separation
- Suspicion for the diagnosis, especially in populations at risk for suicide
- 70% of patients attempting suicide has seen PCP within a month, often „cry for help”
- Thoughts - Contemplating - Plans - Attempt
- If threat of suicide is present, hospital admission should be undertaken

Panic disorder

Frequently present with various somatic complaints

- Palpitations - not paroxysmal, no syncope, no urinating afterwards, no injuries
- Sweating, diaphoresis - on the palms, cold hands
- Trembling or shaking
- Shortness of breath or feeling of smothering
- Choking sensation
- Chest pain or discomfort – stinging pain in the heart
- Dyspnea - no cyanosis, orthopnoe, (hi)cough, sputum, accessory muscle use, no aberration in physical examination of the lungs
- Paraesthesia - perioral, tongue: bilateral, both hands
- Normal serum glucose level

Somatic complaints

- Nausea or abdominal distress
- Feeling dizzy, unsteady, lightheaded, or faint
- Derealisation or depersonalization
- Fear of losing control or going crazy
- Fear of dying
- Parenthesis (i.e., numbness or tingling sensations)
- Chills or hot flashes

Medical disorders

- Angina and myocardial infarction (dyspnea, chest pain, palpitations, diaphoresis)
- Cardiac dysrhythmias (palpitations, dyspnea, syncope)
- Pulmonary embolism (dyspnea, tachypnea, chest pain)
- Asthma (dyspnea, wheezing)

- Hyperthyroidism (palpitations, diaphoresis, tachycardia, heat intolerance)
- Hypoglycemia (sweating, anxiety, tremulousness, palpitation)
- TIA (facial, arm paresthesias)
- Pheochromocytoma (headache, diaphoresis, hypertension)
- Hypoparathyroidism (muscle cramps, paresthesias)
- Seizure disorders

Physical

- The patient may have an anxious appearance.
- Tachycardia and tachypnea are common; blood pressure and temperature may be within the reference range.
- Cool clammy hands may be observed

Therapy

- Education, reassurance (symptoms are neither from a medical condition nor from a mental deficiency. 30-50% placebo response rate)
- Remain empathic and nonargumentative „It's nothing serious" – „It's related to stress"
- Benzodiazepines: immediate antipanic effects (diazepam 10 mg im./iv., alprazolam 0.5 mg po.)
- Long-time treatment: SSRIs, cognitive therapy

Unconscious patient

- Loss of awareness, patient not responding
- Corneal reflex missing
- Breathing and circulation normal
- Check airway, breathing, and pulse; if necessary, rescue breathing and CPR
- If there is no spinal injury → recovery position
- Spinal injury is possible → move the patient only when necessary (vomiting, not breathing)
- Prevent hypothermia

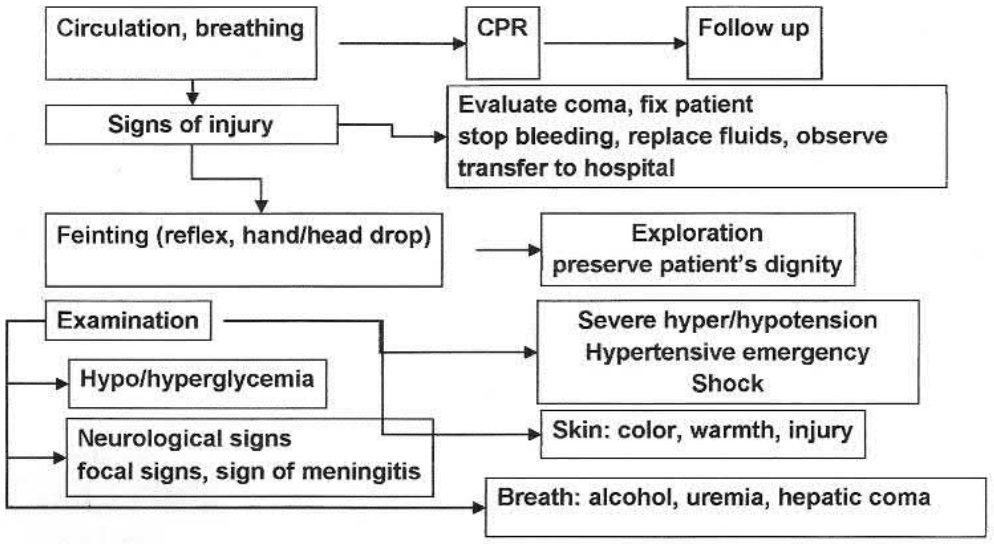
Not to do:

- Hesitate to start CPR, if necessary
- Try to heal immediately
- Place a pillow under the head
- Give water, medications (hypoglycemia)
- Slap the face or splash water onto the face
- Leave alone
- Raise the patient after collapse

Reasons

- Injuries of the head, neck
- Metabolic: hypo/hyperglycemia, hepatic disease, etc.
- Stroke, cerebral tumours, infections
- Epilepsy, psychiatric (conversion, catatonia, hyperventilating)
- Alcohol/substance abuse, poisons

- Brief unconsciousness (fainting): dehydration, low blood sugar, or temporary low blood pressure



Hypovolemic shock

- Fluid loss → circulating volume ↓ → hypoperfusion → multiple organ failure
- Blood loss
- External bleeding
- GI bleeding (varices, ulcers, Mallory-Weiss tears)
- Blood loss into the thoracic and abdominal cavities (solid organ injury, rupture of aortic aneurysm), into the thigh
- Gynecologic cause (ectopic pregnancy, abruption of the placenta)
- Refractory gastroenteritis
- Extensive burns

Signs (moderate → severe)

- Tachycardia
- Delay in capillary refill
- Tachypnoea
- Decrease in pulse pressure
- Cool clammy skin
- Anxiety
- Decreased systolic BP
- Oliguria
- Significant changes in mental status

Pre-hospital care

- Airways, ventilation, circulation
- Direct pressure to external bleeding vessels
- Prevent further injury
    - Cervical spine immobilized

    - Splinting of fractures
    - Move patient to stretcher
- Position (shock position, gravid patient - left side)
- Keep the patient warm, relieve pain
- Start iv. lines (1-2 L lactated Ringer, saline), give oxygen
- Rapid transfer to hospital

Anaphylaxis

Severe allergic reaction with prominent dermal and systemic signs

Causes

- Antibiotics (especially penicillins)
- Other medications (NSAIDs, etc.)
- IV contrast materials
- Insect stings
- Certain foods (peanuts)
- Idiopathic

Signs

Skin, mucous membranes

- Urticaria
- Erythema, pruritus
- Angioedema

Airways

- Nasal congestion, sneezing
- Cough, hoarseness, tightness in the throat
- Dyspnoea (bronchospasm or upper airway oedema)
- Tachypnoea

Anxiety, depressed level of consciousness or agitation

Cardiovascular

- Hypotonia
- Chest pain
- Tachycardia

Gastrointestinal

- Abdominal pain
- Nausea, vomiting
- Diarrhoea

Eye

- Conjunctival injection
- Tearing, itching

Treatment

- Mild symptoms → shock
- Determine respiratory and cardiovascular status
- Skin manifestations may be missing, history of exposure unavailable
- Airway – bag/valve/mask, cricothyrotomy, intubation
- Iv. access (keep vein open → 1 L), oxygen
- Inhaled β-agonists, theophyllin (wheezing)
- Mild reactions → antihistamine
- Epinephrine (systemic manifestations)
- Corticosteroids (delayed effect)

Insomnia. Sleep-related Breathing Disorders

Peter Torzsa MD, PhD

Insomnia is one of the most common symptoms for which adults seek medical advice. In addition to immediate consequences reported by patients, insomnia also precedes or accompanies medical or psychiatric disorders and may occur as a response to physiologic or psychological stressors.

Why do we sleep?

Repair and restoration theory

- sleep enables the body and brain to repair after activity during the day – homeostatic balance
- restore cognitive functioning and memory
- sleep deprivation leads to irritability, impaired concentration and hallucinations
- BUT, how much we sleep does not depend on how much we worked that day

Sleep stages

NREM Sleep

- Stage 1
- Stage 2
- Stage 3
- Stage 4

REM Sleep

ICSD-3

ICSD-3 includes 60 specific diagnoses within the seven major categories, as well as an appendix for classification of sleep disorders associated with medical and neurologic disorders.

Insomnia

1. short-term insomnia,
2. chronic insomnia, and
3. other insomnia (when the patient has insomnia symptoms but does not meet criteria for the other two types of insomnia)

Sleep-related breathing disorders

Central sleep apnea syndromes

1. Central sleep apnea with Cheyne-Stokes breathing
2. Central sleep apnea due a medical disorder without Cheyne-Stokes breathing
3. Central sleep apnea due to high altitude periodic breathing
4. Central sleep apnea due to a medication or substance
5. Primary central sleep apnea
6. Primary central sleep apnea of infancy
7. Primary central sleep apnea of prematurity
8. Treatment-emergent central sleep apnea

Obstructive sleep apnea (OSA) syndromes

1. OSA, adult
2. OSA, pediatric

Sleep-related hypoventilation disorders

1. Obesity hypoventilation syndrome
2. Congenital central alveolar hypoventilation syndrome
3. Late-onset central hypoventilation with hypothalamic dysfunction
4. Idiopathic central alveolar hypoventilation
5. Sleep-related hypoventilation due to a medication or substance
6. Sleep-related hypoventilation due to a medical disorder
7. Sleep-related hypoxemia disorder

Isolated symptoms and normal variants

1. Snoring
2. Catathrenia

Central disorders of hypersomnolence

1. Narcolepsy type 1
2. Narcolepsy type 2
3. Idiopathic hypersomnia
4. Kleine-Levin syndrome
5. Hypersomnia due to a medical disorder
6. Hypersomnia due to a medication or substance
7. Hypersomnia associated with a psychiatric disorder
8. Insufficient sleep syndrome

Circadian rhythm sleep-wake disorders

1. Delayed sleep-wake phase disorder
2. Advanced sleep-wake phase disorder
3. Irregular sleep-wake rhythm disorder
4. Non-24-hour sleep-wake rhythm disorder
5. Shift work disorder
6. Jet lag disorder
7. Circadian sleep-wake disorder not otherwise specified

Parasomnias

NREM-related parasomnias

1. Disorder of arousal from NREM sleep
2. Confusional arousals
3. Sleepwalking
4. Sleep terrors
5. Sleep-related eating disorder

REM-related parasomnias

1. REM sleep behaviour disorder
2. Recurrent isolated sleep paralysis
3. Nightmare disorder

Other parasomnias

1. Exploding head syndrome
2. Sleep-related hallucinations
3. Sleep enuresis

4. Parasomnia due to a medical disorder
5. Parasomnia due to a medication or substance
6. Parasomnia, unspecified

Sleep-related movement disorders

1. Restless legs syndrome
2. Periodic limb movement disorder
3. Sleep-related leg cramps
4. Sleep-related bruxism
5. Sleep-related rhythmic movement disorder
6. Benign sleep myoclonus of infancy
7. Propriospinal myoclonus at sleep onset
8. Sleep-related movement disorder due to a medical disorder
9. Sleep-related movement disorder due to a medication or substance
10. Sleep-related movement disorder, unspecified

Other sleep disorders

Normal sleep and normal aging: our internal clock

The biological clock resides in the brain. It helps regulate when we feel sleepy and when we are alert. It works in tandem with light and dark, and our body temperature and hormones. The National Institute of Health estimates that more than 70 million Americans suffer from sleep problems. The problem escalates with age with the largest users of sleeping pills in the over 65 age bracket. The biggest consumers of hypnotics and tranquilizers are the elderly and we know that prescriptions for sleeping drugs are generally long term.

Insomnia Definitions

Global Sleep Dissatisfaction. Insomnia is first defined by the subject himself, by his persistent complaint (at least 6 months) about the quality or the quantity of his sleep. Four major criteria are commonly used:

1. Difficulty initiating sleep,
2. Difficulty maintaining sleep,
3. Early morning awakening,
4. Non restorative sleep

They must have also daytime consequences.

Insomnia – associated features

At least one (or more) of the following:

- Fatigue or malaise
- Attention, concentration impairment
- Social/ vocational dysfunction/ poor work
- Mood disturbance or irritability
- Daytime sleepiness

Insomnia is not defined by the number of hours of sleep, but rather, by an individual‘s ability to sleep long enough to feel healthy and alert during the day. The normal requirement for sleep ranges between 6 and 10 hours. Insomnia is a symptom, not a disorder by itself.

Types of insomnia

- **Transient insomnia.** < 4 weeks triggered by excitement or stress, occurs when away from home
- **Short-term insomnia.** 4 weeks to 6 months, ongoing stress at home or work, medical problems, psychiatric illness
- **Chronic insomnia.** Poor sleep every night or most nights for > 6 months, psychological factors (prevalence 9%)

Insomnia – assessment

- Determine the pattern of sleep problem (frequency, associated events, how long it takes to go to sleep, and how long the patient can stay asleep)
- Include a full history of alcohol and caffeine intake and other factors that might affect sleep
- Review current medications that patient is taking to eliminate these as possible causes
- Take the history to rule out physical cause and/or psychosocial cause

Possible causes of insomnia

Insomnia – resultant problems

- Reduction in motivation, energy or initiative
- Proneness for errors or accidents at work or while driving
- Tension, headaches or gastrointestinal symptoms in response to sleep loss
- Concerns or worries about sleep
- Secondary psychiatric problems

Medical problems

- Hyperthyroidism
- Arthritis, chronic pain
- Depression
- Benign prostatic hypertrophy
- Headaches; Sleep apnoea
- Periodic leg movement,
- Restless leg syndrome (RLS)

Medications and insomnia

1. Alpha-blockers
2. Beta-blockers
3. Corticosteroids
4. SSRI antidepressants
5. ACE inhibitors
6. ARBs
7. Cholinesterase inhibitors
8. H1 antagonists
9. Glucosamine/chondroitin
10. Statins

Other problems

- Exercise
- Noise
- Light

- Hunger

Health and environment affect our sleep

- Hormonal changes
- Physiological conditions
- Environmental conditions
- Light
- Noise
- Temperature

Management of insomnia

Good sleep history

- Rule out primary psychiatric disorders
- Rule out adverse effects of medications
- Treat underlying causes whenever possible
- Treat underlying depression
- Sleep Diary
- Interventions – CB therapy, medications

Keep a sleep diary to identify your sleep habits and patterns

The following tips can help improve sleep.

- Use the bed only for sleep and sex
- Go to bed at the same time every night
- No daytime napping
- No caffeine, alcohol, or nicotine
- Maintain comfortable sleeping conditions
- Eat at regular times daily (avoiding large meals near bedtime)
- Exercise early in the day
- Get out of bed if you are not asleep after 5-10 minutes and do something else (going to another room may help reduce anxiety about falling asleep)
- Practice evening relaxation routines such as muscle relaxation or meditation
- Medications: non-benzodiazepines drugs

Relaxation training

- Progressive muscle relaxation
- Diaphragmatic breathing
- Autogenic training
- Biofeedback
- Meditation, Yoga
- Hypnosis to ↓ anxiety & tension at bedtime

Benzodiazepine receptor agonists

- Benzodiazepines
- Lorazepam
- Clonezepam
- Temazepam

- Flurazepam
- Quazepam
- Alprazolam
- Triazolam
- Estazolam

Non Benzodiazepines

- Zolpidem
- Zolpidem CR
- Zeleplon
- Eszopiclone

Both these classes act on the GABAA receptors (BzRA) in PCN

Non benzodiazepines

Act at the benzodiazepine receptor. Less risk of dependence

- Zaleplon short ڈife
- Zolipidem, Zopiclone slightly longer ڈife
- No difference in effectiveness & safety
- More expensive

Zolpidem

- Short half life
- Does not produce rebound insomnia
- Low abuse potential
- Less likely to produce withdrawal symptoms
- Rebound insomnia after first night of withdrawal, but soon resolves

Other classes of medications

Antidepressants

- Trazadone
- Mirtazapine
- Doxepin
- Amitryptylin

Antipsychotics

- Olanzapine
- Quitiepine

Melatonin receptor agonists

- Melatonin
- Ramelteon

Miscellaneous

- Valerian
- Diphenhydramine
- Cyclobenzaprine

- Hydroxyzine
- Alcohol

PARASOMNIAS

Parasomnias are a heterogeneous group of sleep disorders that are not strictly speaking abnormalities or dysfunctions of the processes underlying sleep-wake states. The American Classification of Mental Disorders (DSM-V) recognizes only three parasomnias:

- Nightmares
- Night terrors, and
- Sleepwalking

NIGHTMARES

- Associated with various psychiatric disorders.
- Response to antidepressant medications.
- In schizophrenic patients and acute schizophrenic episodes.
- Individuals with a posttraumatic stress disorder may also experience recurrent nightmares about the traumatic event.

SLEEP PARALYSIS

- Transient and generalized inability to move and speak that occur during the transitional period between sleep and wakefulness.
- Episodes vary from one to several minutes and are usually extremely distressing especially when they are accompanied with hypnagogic or hypnopomic hallucinations.
- 30 to 60% of narcoleptic patients.
- Epidemiological studies shown that 6.2% of the general population experienced at least one such episode in their lifetime.
- Moreover, sleep paralysis is often associated with a mental disorder. In some cases, anxiolytic medication may be responsible for this manifestation.

SLEEP BREATHING DISORDERS

The most common sleep disordered breathing disorders:

- Obstructive sleep apnea syndrome (OSAS)
- Central sleep apnea syndrome
- Upper airway resistance syndrome

An obstructive apnea occurs when airflow is absent or nearly absent, but ventilatory effort persists. It is caused by complete, or near complete, upper airway obstruction.

Patients with OSA often have reduced upper airway size due to excess surrounding soft tissue, or a highly compliant airway. The combination of diminished neural output to the upper airway muscles during sleep and reduced upper airway size can result in upper airway collapse, with resulting obstructive apnea [2].

Apnea

- Apnea is the cessation, or near cessation, of airflow. It exists when airflow is less than 20 percent of baseline for at least ten seconds in adults.
- Apnea can produce arousals from sleep, increased arterial carbon dioxide, and decreased oxygen levels.

Hypopnea

- Hypopnea is a reduction of airflow to a degree that is insufficient to meet the criteria for an apnea.
- Airflow decreases at least 30 percent from baseline.
- There is diminished airflow lasting at least ten seconds.
- At least 90 percent of the duration of diminished airflow is spent with airflow that is at least 30 percent less than baseline.
- Decreased airflow is accompanied by at least four percent oxyhemoglobin desaturation.

OBSTRUCTIVE SLEEP APNEA

- More than 15 apneas, hypopneas per hour of sleep (i.e., an AHI>15 events/hr) in an asymptomatic patient, OR
- More than five apneas, hypopneas per hour of sleep (ie, an AHI>5 events per hour) in a patient with symptoms (eg. sleepiness, fatigue and inattention) or signs of disturbed sleep (e.g., snoring, restless sleep, and respiratory pauses).

Epidemiology

- 3-9% have OSAH if defined as an AHI greater than five events per hour accompanied by at least one symptom that is known to respond to treatment (e.g., daytime sleepiness).
- The prevalence of OSAH increases with age. Among patients 65 years and older, there is a two- to three-fold higher prevalence compared to patients 30 to 64 years old [3].
- The estimated prevalence in North America is approximately 20 to 30 percent in males and 10 to 15 percent in females when OSA is defined broadly as an apnea-hypopnea index (AHI) greater than five events per hour as measured by a polysomnogram.

OSA can affect anyone, but is more common in some people, including those who [2]:

- snore loudly
- intermittently stop breathing when sleeping
- are male and middle age
- are a woman past menopause
- are overweight or obese
- have a large neck size (17 inches or more)
- have a small airway
- have a small lower jaw
- have large tonsils, large tongue
- have an abnormal face shape, or nasal blockage

Complications of OSA

Possible C-V Complications of OSA

- Endothelial dysfunction
- Hypertension
- Pulmonary hypertension
- Systolic or diastolic heart failure
- Arrhythmias
- Coronary artery disease
- TIA and stroke

- Dementia
- Death

Diabetes

- OSA is an independent risk factor for diabetes, as it is associated with changes in glucose metabolism which places patients at increased risk of development of type 2 diabetes. Studies have found that the percentage of people living with diabetes who also have OSA to be somewhere between 17 and 48%.
- Evidence also suggests a relationship between OSA, obesity and diabetes: 86% of obese type 2 diabetes patients have OSA. Patients with OSA have an increased prevalence of insulin resistance and type 2 diabetes. While this association can be manifested through shared risk factors such as obesity [4], an independent association between OSA severity, insulin resistance, and type 2 diabetes has been reported in several large cross-sectional studies [5].
- In addition, several longitudinal studies suggest that OSA is a risk factor for incident diabetes, or diabetic complications including diabetic retinopathy, even after adjusting for potential confounders [6, 7].

Car crashes and OSA

- Untreated patients with OSA have higher vehicle collision rate than controls.
- Patients with AHI > 15 (n = 102) have 8.1-fold increased risk of motor vehicle crash compared to matched controls (n = 152)
- Patients with AHI > 34 (n = 78) have 15-fold increased risk of motor vehicle crash than matched controls (n = 160)
- Over 3 years, collision rate in OSA patients treated with CPAP declined to levels similar to those of control subjects [8]

Nonalcoholic fatty liver disease

Intermittent nocturnal hypoxia due to OSA may contribute to the development and severity of nonalcoholic fatty liver disease (NAFLD), independent of shared risk factors such as obesity [9].

DIAGNOSIS

- In-laboratory polysomnography is the first-line diagnostic study when OSA is suspected. However, home sleep apnea testing (HSAT) may be an acceptable alternative for patients who are strongly suspected of having OSA and who do not have medical comorbidities (e.g., heart failure or lung disease) that require more detailed or additional sleep-related measures (sleep stage, arousals, leg and arm movements, seizure monitoring, etc.).
- OSAH exists in asymptomatic adults if the AHI is greater than 15 events per hour and in symptomatic adults if the AHI is greater than five events per hour10.

Polysomnography

- Neurophysiologic variables (electrooculography, EEG, submental myogram) – sleep stages
- Measurement of respiratory effort
- Arterial O_2 sat., pCO_2 – transdermal pulsoxymetry
- ECG
- Limb movements

TREATMENT

- Weight loss [11]

- Positive airway pressure (CPAP)
- Avoidance of alcohol
- Stop smoking
- Oral appliances
- Surgery

RESTLESS LEG SYNDROME (RLS)

- Characterized by disagreeable leg sensations occurring most often at sleep onset that provoke an urge to move the legs.
- An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
- The urge or unpleasant sensations begin or worsen during periods of rest or inactivity.
- Symptoms are partially or totally relieved by movement.
- Symptoms are worse in the evening or at night than during the day [12].

Prevalence of RLS

RLS increased with age. The prevalence of RLS symptoms is close to 20% in elderly people and around 5% for subjects younger than age 30.

Etiology of RLS

- RLS has been also linked with lower serum ferritin levels.
- Uremia is another possible cause for RLS.
- Other factors have also been identified to cause RLS: folate deficiency, vascular insufficiency, chronic obstructive pulmonary disease, gastrectomy, diabetes mellitus and caffeine abuse.

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Tobacco dependence, attitudes and treatment strategies

Peter Vajer MD

Burden of disease

Smoking is highly prevalent worldwide. Smoking increases morbidity and mortality. The benefits of quitting have been demonstrated.

Gender-specific smoking prevalence varies across the world

Worldwide, there are marked differences in smoking prevalence rates between men and women from country to country. For example, in South Africa, the Philippines, China, Iran, and Portugal, smoking prevalence is much lower in women than in men. In contrast, in the United States, Canada, Australia, and Iceland, the prevalence of smoking in men is only slightly higher than that in women (Figure 1.) [1].

Overall, the prevalence of smoking in men is declining. However, although smoking prevalence in women is declining in some countries, such as the United States, the United Kingdom, Australia, and Canada, in several southern, central, and eastern European countries, the rate of smoking in women is not in decline or is still increasing [1].

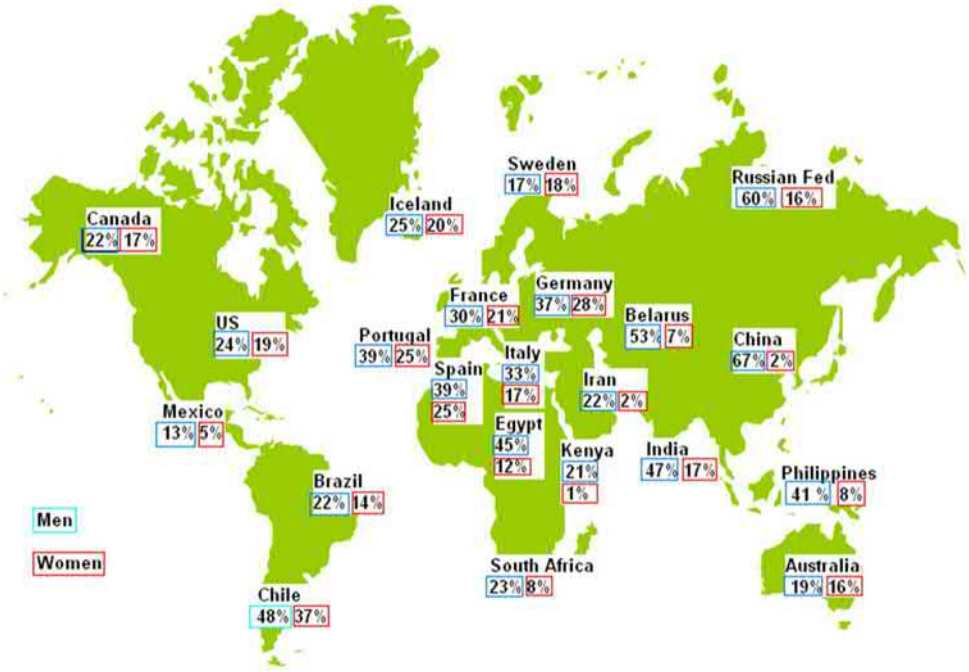


Figure 1. Gender-specific smoking prevalence

Smoking: Leading preventable cause of disease and death

Smoking is causally linked to a host of cardiovascular, respiratory, reproductive, and other conditions, as well as many types of cancer. The top 3 smoking attributable causes of death in the United States are lung cancer, ischemic heart disease, and chronic obstructive pulmonary disease (COPD).

In 2004, the US Surgeon General published a report on the health effects of active smoking, focusing specifically on the evidence for a causal relationship between smoking and disease and death. According to the research summarized in the report, many serious conditions are caused by smoking, including cardiovascular, respiratory, reproductive, and other conditions, as well as cancer affecting diverse areas and organs of the body. In addition to the widely-known consequences of lung cancer

and respiratory disease, smoking has been causally linked to such diverse morbidities as low-bone density, nuclear cataract, bladder cancer, and reduced fertility [2]. Other studies have linked smoking to vascular dementia [3] and peripheral arterial disease [4]. These conditions can affect young and middle-aged smokers and, in general, as a smoker's age increases, the frequency of smoking-caused diseases rises (Table 1.) [2].

Table 1. Smoking: Leading preventable cause of disease and death

Cancer • Lung • Oral cavity/pharynx • Laryngeal • Esophageal • Stomach • Pancreatic • Kidney • Bladder • Cervical • Leukaemia (AML, ALL, CLL) **Cardiovascular** • Ischaemic heart disease • Stroke - Vascular dementia • Peripheral vascular disease • Abdominal aortic aneurysm	**Respiratory** • COPD • Pneumonia • Poor asthma control **Reproductive** • Low-birth weight • Pregnancy complications • Reduced fertility • Sudden Infant Death Syndrome **Other** • Adverse surgical outcomes/wound healing • Hip fractures • Low-bone density • Cataract • Peptic ulcer disease

Annual deaths attributable to tobacco: worldwide estimates

In some countries, deaths attributable to tobacco account for >25% of total deaths in men aged >35 years.

The World Health Organization estimates that in the year 2000, 25% of total deaths in men aged >35 years in most countries in the Northern Hemisphere (including the United States, Canada, Cuba, Israel, Russia and all European nations) were tobacco related. In these countries, >25% of all men died from tobacco-related disorders. Twenty to 25% of women over the age of 35 died from tobacco-related disorders in the United States, Canada, and Cuba (Figure 2.) [1].

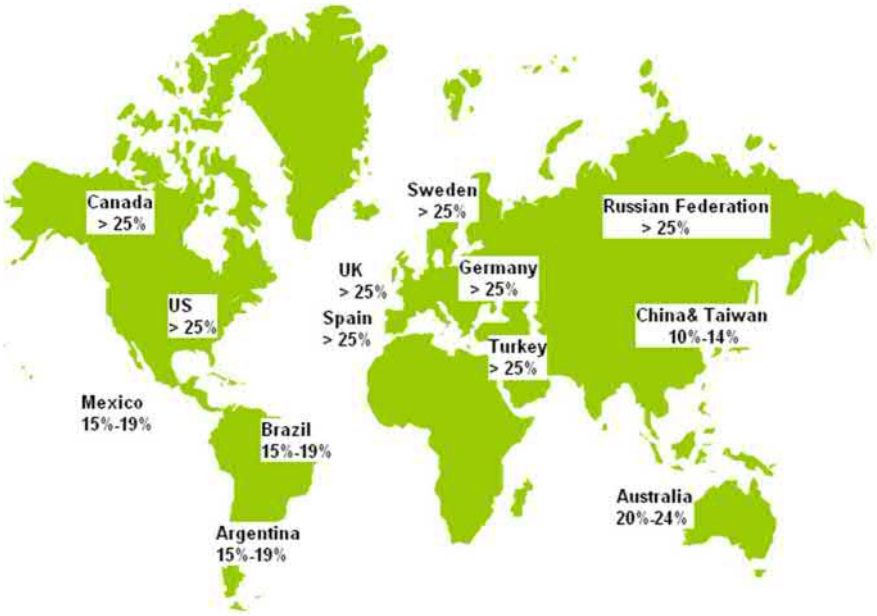


Figure 2. Total deaths attributable to tobacco. Regional estimates in 2000 in men aged >35 years.

Tobacco-related deaths are increasing

Worldwide, millions of people each year die from smoking- and tobacco-related diseases. Recent data show that deaths are equally distributed between developed and developing countries (Figure 3.).

According to the World Health Organization estimates, cigarettes kill half of all lifetime users. In 2000, 4.8 million people worldwide died from tobacco-related illnesses [1]. This figure rose to 4.9 million in 2002 [6]. Although in the past, mortality from tobacco was much higher in developed compared with developing countries, in 2000, the mortality rates were the same (n = 2.4 million) [1]. This represents an exponential increase in tobacco-related mortality in the developing world, rising from negligible levels in 1950, to 0.2 million in 1975, to 2.4 million in 2000. Cigarettes kill half of all lifetime users. Unless young people do not take up smoking and current users quit, tobacco may kill 1 billion people in the 21st century.

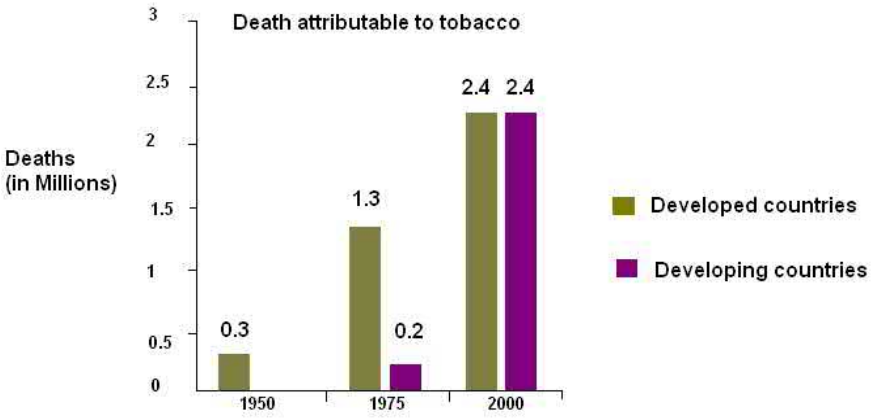


Figure 3. Tobacco-related deaths

Smoking prevalence rates are declining in some countries. However, mortality associated with smoking is increasing since smoking-related mortality is more closely associated with previous tobacco use rather than with current tobacco use.

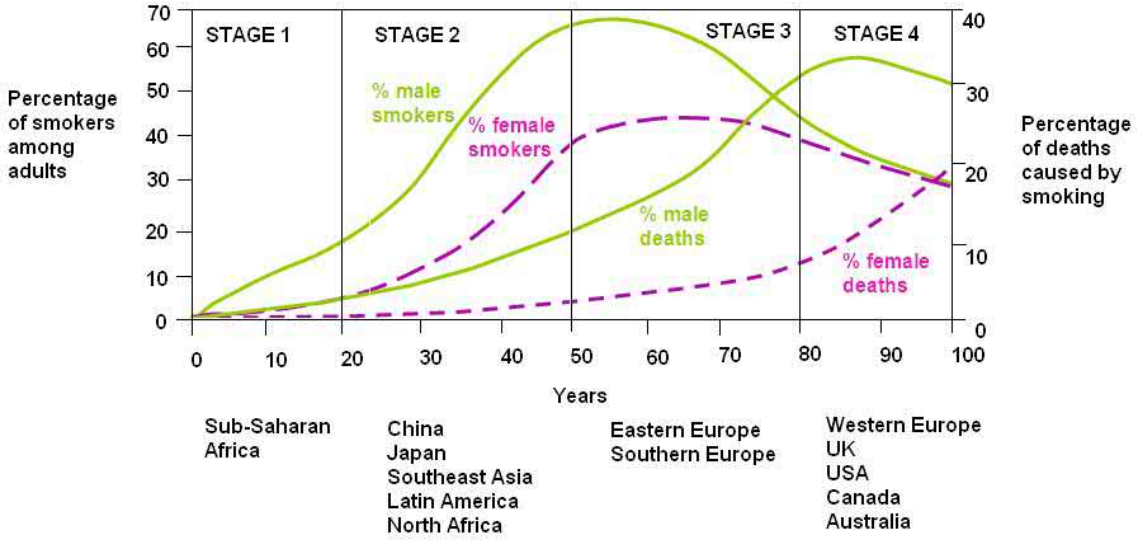


Figure 4. The four stages of the tobacco epidemic: mortality is increasing in many countries

Using data from countries with the longest history of prevalent smoking, Lopez and colleagues constructed a 4-stage model of trends in smoking and subsequent smoking-related mortality (Figure 4.). As the model illustrates, peaks in smoking prevalence in the population do not correspond to peaks in smoking-associated mortality, because current mortality rates are more closely related to previous smoking levels. Therefore, although in some regions, such as Western Europe and North America, smoking prevalence in men and women is on the decline, smoking-related mortality is increasing. Similarly, in areas like Asia, Central and South America, and North Africa, where smoking prevalence rates are increasing, the true impact in terms of smoking-related deaths will not be apparent for several decades [7]. In Asia, where one third of the world's population lives, smoking-related mortality is expected to rise to 4.9 million people annually by 2020 if current smoking trends continue [8].

Smoking reduces survival an average of 10 years

Among male physicians in the United Kingdom, current cigarette smokers died an average of 10 years earlier than lifelong non-smokers (Figure 5.).

This prospective study by Doll et al., used periodically mailed questionnaires to investigate the impact of smoking and of quitting smoking, on the overall mortality of 34,439 male doctors in the United Kingdom from 1951 to 2001. Survival curves for percentage survival from age 35 years for male physicians born in 1900-1930 revealed a 10-year shift in overall survival for those who continued smoking cigarettes vs. lifelong non-smokers. This means that, on average, participants, who never smoked lived 10 years longer than those who were current smokers. By age 70 years, 81% of lifelong non-smokers were alive vs. 59% of continuing cigarette smokers. A mortality rate of approximately 75% was reached at age 80 years for smokers, but was not reached until age 90 years for non-smokers [9].

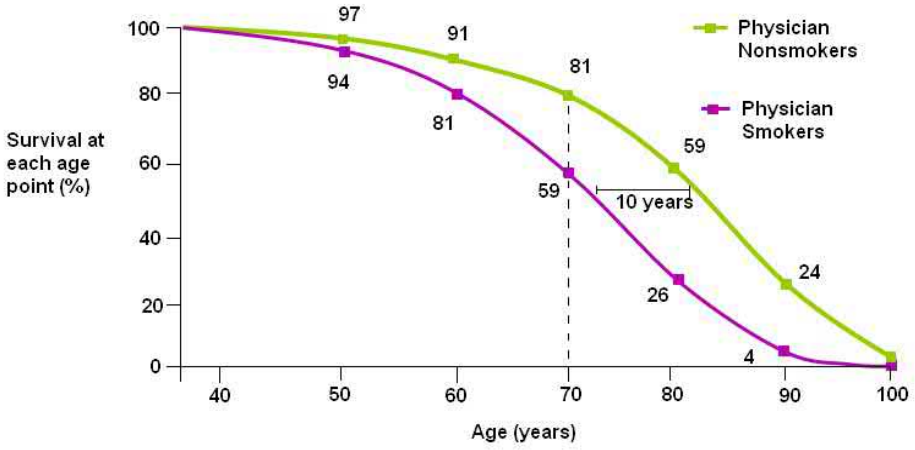


Figure 5. Results from a study of male physician smokers in the United Kingdom [9]

What's in a cigarette?

Tobacco and tobacco smoke are known to be carcinogenic in humans. Tobacco smoke contains at least 4000 chemicals, at least 250 of which are toxic or carcinogenic [10]. For example, tobacco smoke contains irritants, such as acetone, ammonia, and toluene, found in paint stripper, cleaners, and solvents respectively; toxic heavy metals, such as cadmium, used in car batteries, and arsenic, used in poisons; and carbon monoxide, which is a hazardous component of exhaust fumes (Table 2.) [1]. Although it is addictive, the nicotine found in tobacco is not a known carcinogen [11]. All cigarettes are toxic: the US Surgeon General's report noted that smoking cigarettes with lower yields of tar and nicotine provides no health benefit [12].

Table 2. Chemicals in tobacco smoke

Chemical in tobacco smoke	Also found in…
• Acetone	• Paint stripper
• Butane	• Lighter fluid
• Arsenic	• Ant poison
• Cadmium	• Car batteries
• Carbon monoxide	• Car exhaust fumes
• Toluene	• Industrial solvent

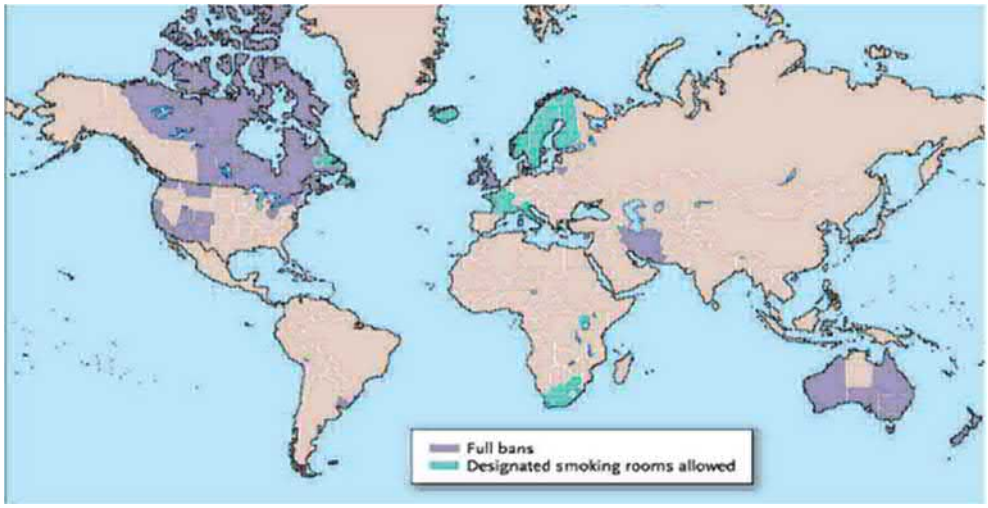
Mechanisms of action: how smoking causes disease

The pathological mechanisms of smoking include those specifically linked to the pathogenesis of diseases and those that are less specific. For example, smoking directly exposes lung cells to the potent mutagens and carcinogens, which cause genetic changes in lung cells associated with lung cancer development. Smoking causes or contributes to endothelial injury and dysfunction, prothrombotic/fibrinolytic effects, inflammation, and adverse lipid profiles, which lead to cardiovascular disease. Finally, biological processes resulting in airway and alveolar injury and the accelerated decline in respiratory function caused by smoking contribute to the development of COPD [2].

Second-hand smoking

1973: Arizona becomes the first state to pass a law restricting smoking in public places (including elevators, libraries, indoor theatres and concert halls, and buses).

1975: Minnesota enacts the nation's first law requiring either separate smoking areas or no smoking in most public places, including restaurants.



ountries, states, and provinces that have banned smoking in indoor workplaces and other indoor public places [Koh HK et al. Making smoking history worldwide. NEJM 356:1496. (2007)].

What does second-hand smoke do?

Second-hand smoke is a serious health hazard. According to the US Surgeon General's 2006 report, there is no risk-free level of exposure to second-hand smoke. This recent report, as well as data from the World Health Organization, estimate exposure to second-hand smoke in non-smokers increases lung cancer risk by 20%-30% [1, 2]. In adults, second-hand smoke exposure may also worsen existing lung disease, such as asthma, COPD, and emphysema [1]. Environmental smoking can induce and exacerbate asthma in children and can cause middle ear disease and otitis media [1].

A study in 52 countries showed that second-hand smoke increases risks of nonfatal acute myocardial infarction. The risk was increased in a graded manner, and the effect was most marked in subjects who never smoked and former smokers. The overall attributable risk was 15.4% in subjects who never smoked but are exposed for ≥1 hour per week to second-hand smoke compared with those who never smoked and never were exposed [13]. The 2006 US Surgeon General's report notes that second-hand smoke exposure increases the risk of heart disease by 25%-30% in non-smokers [2].

What does second-hand smoke do to infants and children?

A large percentage of children in the US are exposed to second-hand smoke. In the United States, nearly 60% of children aged 3-11 years (almost 22 million) are exposed to second-hand smoke, and approximately one quarter of children in this age group live with a person who smokes. In comparison, only 7% of non-smoking US adults live with a person who smokes [14]. In some countries (e.g. Hungary, Romania, and Estonia), the percentage of youth who live in a home where others smoke in their presence is 80% and above [1].

As evidenced by data from several countries, exposure to second-hand smoke in infants and children is associated with an increased risk of disease and hospitalisation [15-17]. Annually, 17,000 children aged <5 years are hospitalised in the United Kingdom for diseases caused by second-hand smoke [15]. One study conducted in 4486 infants in Tasmania, Australia found that compared with the risk in infants of mothers who smoked after pregnancy but never in the same room with their infants, the risk of infant hospitalisation was 56% higher if the mother smoked in the same room, 73% higher if the mother smoked when holding the infant, and 95% higher if the mother smoked when feeding the

infant [16]. A study in Hong Kong similarly found an increased likelihood for hospitalisation in infants living with any smoker at home who smoked in close proximity to the infant (<3 metres) compared with infants who lived in a smoke-free home [17].

Smoking during pregnancy. Harms infants

Exposure to tobacco smoke during pregnancy is associated with serious consequences for infants and children. Environmental smoke is associated with a 4-fold increased risk of low-birth weight and an increased risk of miscarriage, stillbirth, and sudden infant death syndrome (SIDS) [15, 18]. Annually in the United States during the 1990s, 9,700-18,600 cases of low-birth weight infants were related to secondhand smoke [1]. In addition, lung function may be impaired, and a possible association with cognitive and developmental syndromes may exist [19].

Why quit? Potential lifetime health benefits of quitting smoking

When gauging the health benefits from smoking cessation one is encouraged to assess both the short-term and long-term improvements. Within 2 weeks to 3 months lung function may begin to improve and there may be notable decreases in coughing, sinus congestion, fatigue and shortness of breath.

Around the year mark, coronary heart disease risk, the leading cause of death in the United States, improves with smoking cessation to a point where excess risk is reduced by 50% and continues to decline thereafter. Within the 5-15 year range, the risk of stroke for smoking cessators returns to the level of a person who has never smoked.

Other potential long-term benefits include that the risk of lung cancer, the most common cause of cancer death in the United States, declines steadily after smoking cessation. By 10 years after cessation, the risk of lung cancer is 30-50% that of continuing smokers. And beyond this, smoking cessation may also reduce the risk of cancers of the larynx, oral cavity, oesophagus, pancreas, urinary bladder and of developing ulcers of the stomach or duodenum. Other long-term benefits include the rate of decline in lung function among former smokers returns to that of never smokers, reducing the risk of COPD. The risk of coronary heart disease, after 15 years of abstinence, becomes similar to that of a person who has never smoked. Clearly, a patient has health benefits to gain if they successfully cessate (Figure 7.) [20-22].

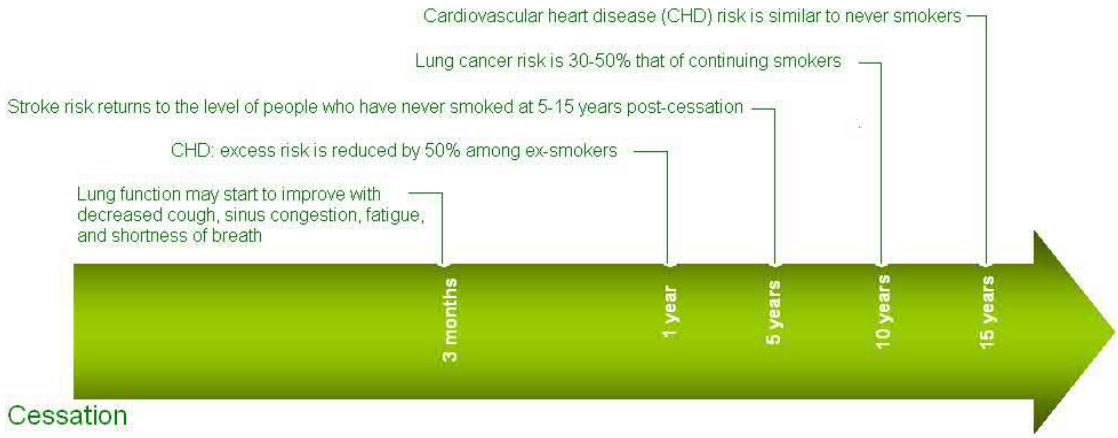


Figure 7. The potential lifetime health benefits of quitting smoking

Quitting at any age may increase life expectancy (Figure 8., 9., 10.). Results from a study of male physician smokers in the United Kingdom. Quitting sooner appears most beneficial [9].

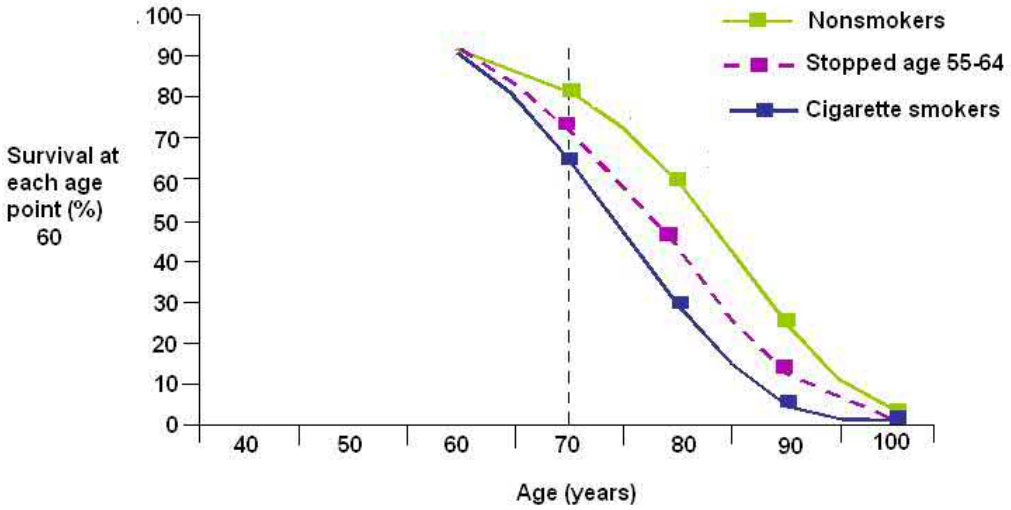


Figure 8. Quitting at age 55-64.

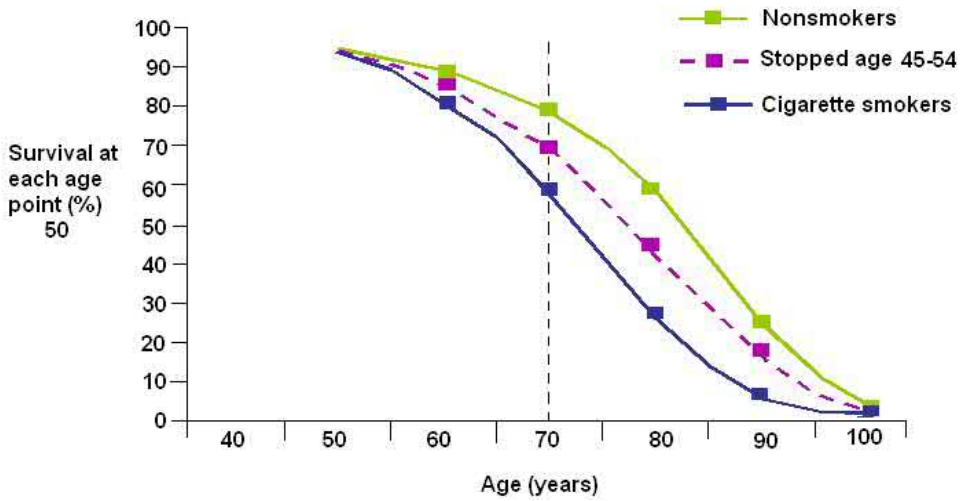


Figure 9. Quitting at age 45-54.

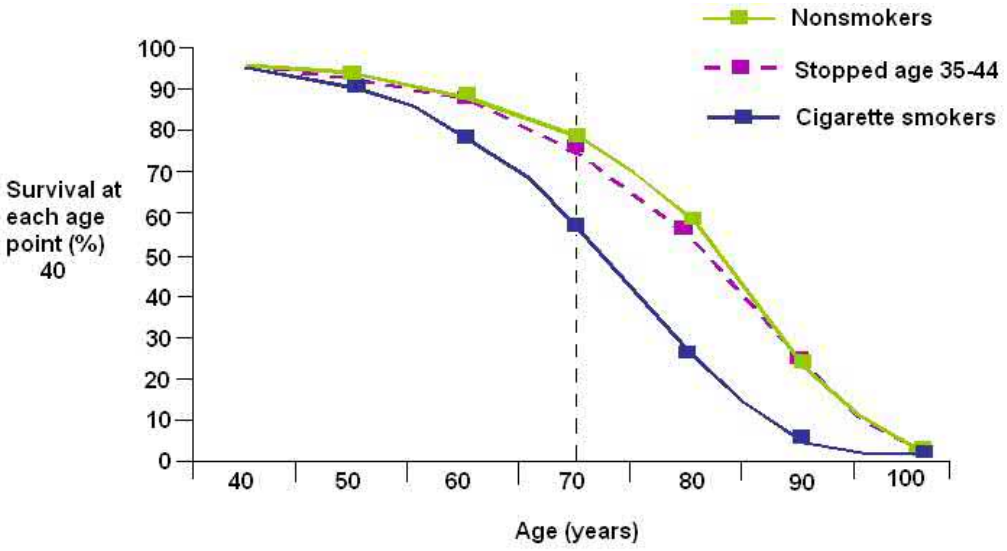


Figure 10. Quitting at age 35-44.

In summary, smoking prevalence and attributable deaths are enormous and in some areas increasing. Smoking is leading preventable cause of disease and premature death. Second-hand smoke linked with deadly diseases-infants and children at special risk. Quitting improves health outcomes and can reverse disease progression.

Tobacco dependence mechanisms

- Nicotine's actions in the central nervous system.
- Neurobiologic and physiologic effects of tobacco dependence.
- Tobacco dependence and environmental reinforcement.
- Symptoms of withdrawal.

Mechanism of action of nicotine in the central nervous system

After inhalation, nicotine preferentially binds to nicotinic acetylcholinergic (nACh) receptors located in the mesolimbic-dopamine system of the brain within a matter of seconds. Nicotine specifically activates α4β2 nicotinic receptors in the Ventral Tegmental Area (VTA) causing an immediate dopamine release at the Nucleus Accumbens (nAcc). The dopamine release is believed to be a key component of the reward circuitry associated with cigarette smoking (Figure 1) [23].

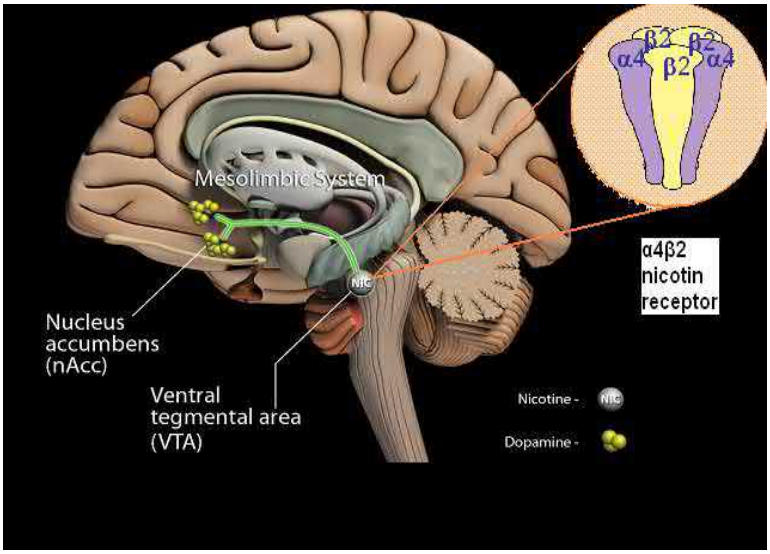


Figure 1. Nicotine action at the central nervous system

Nicotine activates α4β2 nicotinic receptors that are localized to the neuronal bodies and terminal axons of the cells in the ventral tegmental area. This activation thereafter causes dopamine release at the nucleus accumbens, which is believed to result in the short-term reward/satisfaction effect associated with cigarette smoking (Figure 2.) [23].

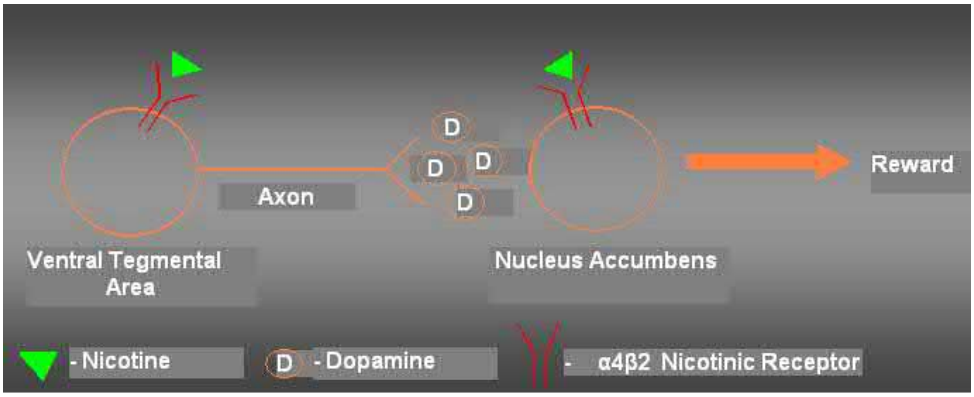


Figure 2. Nicotine stimulates dopamine release

Tolerance typically develops after longer-term nicotine use. Tolerance is related to both the up-regulation (increased number) and the desensitization of nicotinic receptors in the VTA that occurs as a result of long-term exposure to nicotine. A drop in nicotine level, in combination with the up-regulation and decreased sensitivity of the nicotinic receptor can result in withdrawal symptoms and cravings. Smokers have the ability to self-regulate nicotine intake by the frequency of cigarette consumption and the intensity of inhalation [24]. In order to maintain a steady nicotine level, smokers generally titrate their smoking to achieve maximal stimulation and avoid symptoms of withdrawal and craving [25].

The cycle of nicotine addiction

The distribution of nicotine is very rapid. It can reach the brain within 10 to 20 seconds after inhaling cigarette smoke [25]. The binding of nicotine to its relevant receptors results in the release of multiple neurotransmitters, most critically dopamine. The release of dopamine in the nucleus accumbens neurons is thought to play a critical role in the addictive nature of nicotine. This release of dopamine requires binding of nicotine to α4β2 receptors (Figure 3.) [23, 25].

Absorption of cigarette smoke from the lungs is rapid and complete, producing with each inhalation a high concentration of arterial nicotine that reaches the brain within 10 to 16 seconds. Nicotine has a terminal half-life in blood of 2 hours. Smokers therefore experience a pattern of repetitive and transient high blood nicotine concentrations from each cigarette. Nicotine's activation of acetylcholinergic receptors induces the release of dopamine in the nucleus accumbens. This is similar to the effect produced by other drugs of misuse, such as amphetamines and cocaine. The symptoms of nicotine withdrawal are a major barrier to smoking cessation. Smokers start to experience impairment of mood and performance within hours of their last cigarette. These effects are completely alleviated by smoking a cigarette. Withdrawal symptoms include irritability, restlessness, feeling miserable, impaired concentration, and increased appetite, as well as craving for cigarettes. Cravings, sometimes intense, can persist for many months.

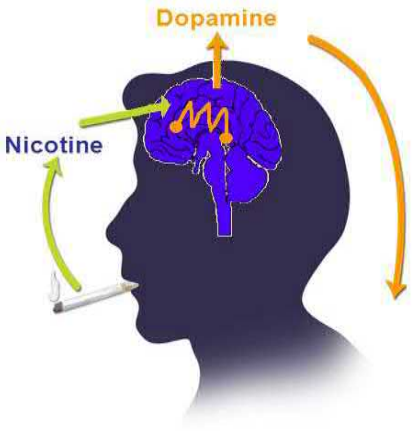


Figure 3. The cycle of nicotine addiction [3].

Nicotine is at least as strong of an addiction as drugs of abuse

In the past there was some controversy regarding whether smoking was a dependency or an addiction. However, it is now generally agreed that nicotine is at least as strong of an addiction as drugs of abuse [25]. The use of nicotine results in significant changes in the brain that make people want to smoke, regardless of the deadly potential of long-term smoking. Long-term smoking also causes unpleasant psychologic and physiologic withdrawal symptoms when individuals stop [25].

Historically, nicotine addiction has been one of the hardest substance-use dependencies to break. The 1988 Surgeon General's Report, Nicotine Addiction, concluded that: “Cigarettes and other forms of tobacco are addicting. Nicotine is the drug that causes addiction and that the pharmacologic and behavioural characteristics that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine” [4]. According to this report, certain criteria must be met before a drug can be classified as addictive. The criteria are primary: highly controlled or compulsive use, psychoactive effects (e.g., pleasure), and drug-reinforced behaviour. Other additional criteria include: addictive behaviours (i.e., stereotypical patterns of drug use, drug use despite known harmful effects, relapse after drug use is stopped, and recurrent drug cravings, dependence-producing effects (i.e., tolerance, physical dependence, and pleasant effects - euphoria) [26].

Cigarette smoking is a chronic relapsing medical condition

Tobacco dependence is a chronic condition with addiction comparable to that caused by other drugs of abuse [25]. Long-term clinical intervention for nicotine addiction is needed, just as it is for other addictive disorders. Clinicians may fail to appreciate the chronic nature of nicotine addiction and, therefore, fail to treat smoking consistently and over the long term. It should be considered a chronic condition, such as diabetes, hypertension, or hyperlipidaemia, and treated as such. Smoking is a relapsing condition, and it is easy to understand why the vast majority of smokers who attempt to quit fail over multiple attempts [27].

Smoking cessation and weight gain

Numerous studies have found evidence that smoking cessation is associated with weight gain, yet therapeutic approaches, including dietary strategies and exercise may help to limit this gain and result in more patients willing to quit.

Klesges et al. investigated the magnitude of weight gain in a cohort using both point prevalence and continuous abstinence criteria for cessation [28]. Continuous abstinence refers to those participants

who quit smoking and maintain abstinence throughout the follow-up period. In contrast, point prevalence abstinence refers to smoking (yes vs. no) at a particular follow-up period, with no correction for previous or subsequent relapses to smoking.

Participants were 196 volunteers in a smoking cessation program, who continuously smoked (n = 118), were continuously abstinent (n = 51), or were point prevalent abstinent (n = 27) (i.e., quit at the 1-year follow-up visit but not at other visits). Continuously abstinent participants gain over 5.9 kg at 1 year, significantly more than continuously smoking and point prevalent abstinent participants (1.1 kg and 3.04 kg, respectively). Of note, participants did not gain weight at a constant rate across the 1-year follow-up (Figure 4.) [28].

Ultimately, steps, including dietary strategies and exercise, can be taken to prevent weight gain after quitting and these steps might result in more patients willing to quit [29].

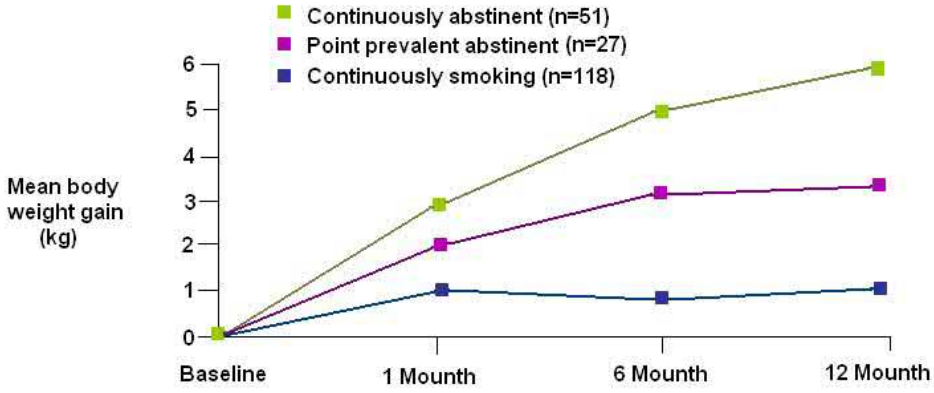


Figure 4. Smoking cessation and weight gain

Tobacco dependence and environmental behaviour reinforcement

Both animal and human experiments suggest that the direct pharmacologic effects of nicotine are necessary, but not sufficient, to explain tobacco dependence. Non-pharmacologic factors also play a critical role in smoking behaviours. Nicotine rapidly delivered to the brain is a primary reinforcer of smoking (pharmacologic effects). However, environmental/social stimuli associated with smoking (non-pharmacologic effects) are also important. The pharmacologic and non-pharmacologic aspects of this process may be synergistic: the reinforcing effects of environmental/social stimuli are believed to be strengthened by nicotine [30].

The withdrawal syndrome

Recognizing that nicotine withdrawal results in clinically significant impairment in a person's ability to function, the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) classifies these symptoms as a distinct condition: nicotine withdrawal syndrome (Figure 5.). The symptoms of nicotine withdrawal syndrome can develop rapidly after a smoker tries to quit, and characteristics include the psychological symptoms of dysphoric or depressed mood, anxiety, irritability, frustration, or anger; and restlessness or impatience and the physical symptoms of insomnia, increased appetite/weight gain, and difficulty concentrating. Although present in those who use other nicotine-containing products, the manifestations of nicotine withdrawal syndrome are more intense in individuals who smoke compared with those who use other forms of tobacco [31]. The rapidity of onset and intensity of withdrawal syndrome in smokers may suggest a greater dependence on tobacco. The typical duration of most of these symptoms is <4 weeks. Increased appetite is an exception, often lasting for >10 weeks. Although anxiety is listed as a classic symptom of nicotine

withdrawal in the DSM, additional information is available about the relationship between anxiety and smoking. Some evidence suggests that while smokers increase their smoking when stressed, smoking does not help relieve the stress. As smokers stop smoking, levels of stress and anxiety actually decrease [32].

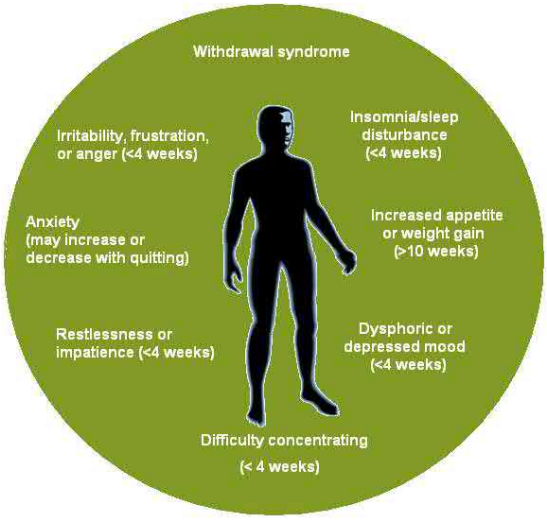


Figure 5. The withdrawal syndrome: a combination of physical and psychological conditions, making smoking hard to treat.

Summary

- Nicotine in cigarettes is highly addictive.
- The physical and psychological rewards of smoking reinforce repeat behaviour.
- Environmental stimuli also trigger smoking behaviours.
- When quitting, cigarette smokers experience cognitive, affective, and physiologic changes.

Current approaches to treatment of tobacco dependence

- The patients' perspective
- The physicians' role
- Non-pharmacologic therapies
- Pharmacologic therapies
- Varenicline efficacy and safety data

Leading health organizations from around the world recognize the physician's role in helping their patients to quit smoking

Physicians play an instrumental role in motivating their patients to quit smoking. Several worldwide leading health organizations have acknowledged this role in statements encouraging physicians to become active promoters of smoking cessation by not only talking to their patients about quitting smoking but also in leading by example. The Tobacco Free Initiative of the WHO notes that "health workers function as exemplars and educators for their patients, and consequently should set an example by abstaining from tobacco" [33]. For patients, "physician advice does increase both immediate and more distant attempts to quit." This sentiment is echoed by several other organizations, including the American Medical Association, Health Professionals Against Smoking, and the American Academy of Family Physicians, which "strongly encourages all of its members and staff to personally avoid tobacco use" as well as to provide cessation counselling and other types of therapies to patients to assist them in quitting smoking [34, 35]. A statement from the National

Institute for Health and Clinical Excellence further reinforces the physician's role in smoking cessation interventions by characterizing the evidence in support of physician advice as "level 1+". In that this recommendation is supported by a review of the clinical trials evidence and that sufficient criteria have been met so as not to bias the conclusions [36].

Regardless of motivation level, all smokers should be actively offered assistance to quit

The Intervention 1999 study is a large, ongoing, randomized, population-based smoking intervention study in Copenhagen, Denmark. This study is investigating the impact of smoking cessation assistance offered on a group basis to smokers at various levels of motivation to quit. At enrolment 11,708 smokers were randomized to the high-intensity intervention group, 1,308 entered a low-intensity intervention group, and 48,285 received no intervention, of whom 5,264 served as the control group. All study participants received a lifestyle consultation. In the high-intensity intervention group, 2,168 smokers were offered group assistance to quit, 575 accepted, and 408 attended at least 1 session over the course of a year. Of this subset, about 35% were continuously abstinent at the end of the quitting smoking group session (17 weeks). Only 16% of abstinent smokers had indicated plans to quit (84% had no plans to quit) before the lifestyle consultation. Motivation to quit before the lifestyle consultation did not consistently predict abstinence, and a number of smokers in the early motivational stages were able to achieve sustained abstinence [37].

Why some smokers may need more help to quit

The US Community Intervention Trial for Smoking Cessation (COMMIT) study followed 6,603 individuals who were current smokers in 1988 for 13 years. Participants completed detailed telephone surveys on tobacco habits (in 1988, 1993, and 2001) and were asked questions about methods and reasons for quitting smoking (in 1993 and 2001). Individuals who reported that they had not smoked for ≥6 months before completing the survey were categorized as former smokers. The investigators conducted a logistic regression analysis to assess the association between the characteristics of smokers and success of quitting smoking. They found that higher levels of nicotine dependence (assessed by cigarette count and time to first cigarette upon awakening) and living with at least 1 other smoker were both associated with a decreased likelihood of quitting smoking [38].

In the British Household Panel Survey, over 10,000 adults were interviewed, with approximately 30% reporting smoking cigarettes. Chandola et al. investigated socio-demographic factors among this population and their relation to successful smoking cessation. All the socio-demographic variables were significantly associated with quitting smoking. Respondents in the small employer, supervisor, and routine occupational classes were less likely to quit compared to professional respondents. In addition, those living in more deprived wards, having fewer educational qualifications, or lower household incomes were less likely to quit [39].

Kalman et al. reviewed the comorbidity of smoking with psychiatric (PD) and substance use disorders (SUD) [40]. They note that an important subset of refractory smokers is those with PD or SUD, among whom smoking rates exceed those in the general population by two- to fourfold. Among "ever smokers," persons with PD or SUD are less likely to be former smokers than other smokers. Significantly lower quit rates are associated with several specific PD and SUD, including alcohol use disorder, bipolar disorder, major depression, and post-traumatic stress disorder [40].

Multiple quit attempts may be necessary

Unrealistic expectations about quitting attempts are a prime obstacle for both patients and physicians. Epidemiologic data indicate that >70% of smokers in the United States have tried to quit smoking at least once, and about 46% of US smokers try to quit each year [41]. Similar percentages

are seen in countries with established tobacco control programs, such as the United Kingdom, Australia, and Canada, where >70% express a desire to quit, and 30%-50% try to quit annually [42]. Unfortunately, most of these quit attempts are unsuccessful: in 1991, of the 17 million US adults who tried to quit smoking, only 7% were not smoking 1 year later [41].

However, past failure does not prevent future success. This is illustrated by the findings of Grandes et al., who studied smokers attending 7 smoking intervention (n = 1,203) and 3 control (n = 565) practices in Spain for 1 year [11]. They found that previous attempts to stop smoking (≥3 months in duration) was a positive predictor for quitting success (adjusted OR = 1.8) [43].

Most smokers are willing to try again

Joseph et al investigated the willingness to try to quit again in smokers who recently had an unsuccessful quit attempt [44]. The study population was comprised of a random sample of a total of 2,340 smokers from the Minneapolis Veterans Administration Medical Center (n = 391) who received prescriptions for any smoking cessation therapy available at that time. Participants completed a structured telephone survey a minimum of 3 months after receiving the prescription. At 1 month, the point-prevalent abstinence rate was 19.7%. Of those who continued to smoke, 98% were willing to make another quit attempt: 50% indicated they were willing to try to quit again immediately, and 28% within 1 month [44].

Length of prior abstinence is related to quitting success

Smokers with repeated quit attempts of longer duration have a higher likelihood of successfully quitting smoking. A non-randomized, controlled study examined predictors of smoking abstinence in 1,768 patients attending primary health care centres in Spain. Smokers either attended 7 stop smoking intervention practices (n = 1,203) or 3 control practices (n = 565), and follow-up occurred between 12 and 24 months after the patient visited the practice. Biologically confirmed sustained abstinence was observed in 7.3% of smokers who attended the intervention practices (5% in those who received a self-help handout and advice, 16% of those who also received follow-up, and 22% who received the handout, advice, follow-up, and the nicotine replacement therapy patch). Previous attempts to stop smoking for ≥ 3 months were a positive predictor of quitting success (adjusted OR, 1.8; 95% CI, 1.1-2.7) [43].

A multicentre, randomized, double-blind study conducted in 74 outpatient clinics for quitting smoking in France investigated the efficacy of 7 weeks of treatment with bupropion SR versus placebo in 509 smokers, followed for 26 weeks post treatment. The results showed that longer duration of previous quit attempts, as well as absence of smoking-related disease and low level of current alcohol problems, among other characteristics, were predictive of successfully quitting smoking [45].

Non-pharmacologic therapies: advice and support

Even brief intervention for quitting smoking can be effective, and every smoker should be advised to quit. Based on extensive research of published trials, the recommendations from the US Department of Health and Human Services Clinical Practice Guideline for treating tobacco use and dependence emphasize the importance of person-to-person interaction, finding that these treatments (e.g., individual, group, or proactive telephone counselling) are consistently effective in helping smokers to quit. Not all approaches are appropriate for all smokers, and clinicians should, when possible, direct smokers to the best form of treatment available depending on the individual needs of the patient and access to available resources. There is a dose-dependent relationship between the intensity of tobacco-dependence counselling and its effectiveness. Nevertheless, whether intervention is brief or

intensive, the same 3 types of counselling and behavioural therapies are especially effective and should be used with all patients attempting to quit: 1) practical counselling, which comprises problem solving and skills training; 2) social support as part of treatment; and 3) social support outside of treatment [41, 46].

Tobacco dependence support: the "5As"

Physicians need to proactively engage with patients to provide medical interventions to improve quitting success rates. The US Department of Health and Human Services Guidance on Treating Tobacco Use and Dependence recommends physicians use an intervention model incorporating the "5As": ask advice, assess, assist, and arrange follow-up. The first step is to identify and document tobacco use for every patient at every visit by asking them about their tobacco use. For current smokers, the next steps are to first advise them to quit in a clear, strong, and personalized manner, and then assess their willingness to do so at this time. Physicians should educate those who are unwilling to quit about tobacco's harmful effects; they should reassure patients who have fears or concerns about quitting or feel demoralized because of a failed previous quit attempt. Those who are or who become willing to quit should be assisted with quitting, including appropriate counselling and pharmacotherapy (unless special circumstances do not allow for pharmacologic intervention). Finally, arranging an initial follow-up with smokers soon (preferably within 1 week) after the quit date and a second follow-up within a month of quitting is important to support the patient and promote the success of the attempt [41]. The "5As" are as follows:

1. Ask about tobacco use
2. Advise to quit
3. Assess willingness to make a quit attempt
4. Assist in quit attempt
5. Arrange follow-up

The first step in an intervention incorporating the 5A model is to identify and document tobacco-use status for every patient at every visit by asking them about their tobacco use. Through the implementation of an office-wide system, physicians can ensure that tobacco use status is queried and documented for EVERY patient at EVERY visit. One suggestion is to expand the vital signs record to include tobacco use, or to use an alternate universal identification system. Alternatives to expanding the vital signs are to place tobacco-use status stickers on all patient charts or to indicate tobacco use status using electronic medical records or computer reminder systems [41].

The second step in an intervention incorporating the 5A model is to advise all current smokers to quit in a clear, strong, and personalized manner. Examples of clear statements include, "I think it is important for you to quit smoking now, and I can help you," and "Cutting down while you are ill is not enough." The following is a representative example of a strong statement: "As your clinician, I need you to know that quitting smoking is very important to protecting your health now and in the future. The clinic staff and I will help you." Personalization of the advice includes tying tobacco use to current health/illness, its social and economic costs, motivation level/readiness to quit, and/or the impact of tobacco use on children and others in the household [41].

The third step in the 5A intervention model is assessment of the willingness of current smokers to make a quit attempt at the present time. Physicians should educate those who are unwilling to quit about tobacco's harmful effects, motivate them to want to quit, and reassure them should they have fears or concerns about quitting or feel demoralized because of failed previous quit attempts. If the smoker is willing to make an attempt to quit at the present time, assistance should be provided. If

the patient is willing to participate in intensive treatment, such treatment should be delivered or a referral for intensive intervention should be made [41].

The fourth step in the 5A intervention model is to assist those who are or who become willing to quit, including appropriate counselling and pharmacotherapy (unless special circumstances do not allow for pharmacologic intervention). Assisting willing patients involves making a quit plan by setting a date to stop smoking, telling family and friends (to elicit understanding and support), anticipating challenges with quitting (withdrawal symptoms), and removing tobacco products from the environment. Practical counselling is an important part of cessation assistance. The physician should emphasize total abstinence, draw from previous experience with quitting, help the smoker understand triggers and challenges, encourage abstinence from alcohol, and explain the importance of having housemates and family members quit smoking, as well. The physician should provide a supportive clinical environment and offer assistance in the development of a social network to support the quit attempt. In regard to pharmacotherapy, use of approved medications should be recommended, except in special circumstances, with an explanation of how these drugs may increase smoking cessation success and reduce withdrawal symptoms. The provision of supplementary materials should accompany all quit attempts. These materials are available from federal agencies, non-profit agencies, or local/state health departments. They should be culturally/racially/educationally/age appropriate for the patient and readily available at every clinician's workstation [41].

The final step in the 5A model is to arrange an initial follow-up with the patient soon (preferably within 1 week) after the quit date and a second follow-up within a month of quitting. This is important in supporting the patient and promoting the success of the attempt. After the second follow-up contact, additional follow-ups occur as needed, either in person or via telephone.

During the follow-up visit, the clinician should congratulate success. If tobacco use has occurred, review the circumstances and elicit a recommitment to complete abstinence. Remind the patient that a lapse can be used as a learning experience. The clinician should help the patient identify problems already encountered and anticipate challenges in the immediate future. Pharmacotherapy use and issues associated with quitting should be assessed during the follow-up meeting, and consideration of provision or referral to more intensive treatment should be given [41].

Session length was categorized based upon the maximum amount of time the clinician spent with a smoker addressing tobacco dependence in a single contact. These levels of person-person contact were compared to no contact (e.g. self-help only). The data indicates that there is a dose-response relationship between session length and abstinence rates whereby higher intensity counselling produced higher abstinence rates than either minimal or low intensity counselling (Table 1.).

Table 1. Effectiveness increases with treatment intensity

Level of Contact	**Estimated Odds Ratio (95% CI)**	**Estimated Abstinence Rate (95% CI)**
No Contact	1.0	10.9
Minimal Counselling (less than 3 minutes)	1.3 (1.01 - 1.6)	13.4 (10.9 - 16.1)
Low Intensity Counselling (3 to 10 minutes)	1.6 (1.2 - 2.0)	16.0 (12.8 - 19.2)
Higher Intensity Counselling (more than 10 minutes)	2.3 (2.0 - 2.7)	22.1 (19.4 - 24.7)

Non-pharmacologic treatment for smoking cessation

A number of Cochrane reviews have analysed the efficacy of non-pharmacological interventions for quitting smoking over a minimum of 6 months, including self-help with tailored or standard materials [47], telephone counselling [48], group [49] and individual [50] counselling, and physician advice [51]. These methods have been tested in thousands of smokers (Table 2.). In general, all are more effective compared with no intervention [47-51]. The OR for self-help materials versus no intervention (n = 11 trials) was 1.24. Self-help materials that were tailored for the characteristics of individual smokers were slightly more effective compared with standard materials (OR = 1.42; n = 17 trials) [48]. Both telephone (n = 13 trials) and individual counselling (n = 17 trials) yielded an OR of 1.56 compared with less intensive/minimal interventions [16, 18]. Group therapy was the most effective non-pharmacological intervention, with an OR of 2.04 vs. self-help (n = 16 trials) and 2.17 versus no intervention (n = 7 trials), but was tested in the fewest number of patients: 4,395 and 815 patients, respectively [49]. Analysis of the trials investigating physician advice as an intervention found that even brief advice was effective in increasing the OR for quitting smoking (1.74; n = 17 trials) [51].

Table 2. Non-pharmacologic treatment for smoking cessation

Comparison	N Trials	N Participants	Pooled OR* (95% CI)
Physician's advice [15]			
Brief vs. no advice (usual care)	17	>13,000	1.74 (1.48 – 2.05)
Intensive vs. minimal advice	15	>9,000	1.44 (1.24 – 1.67)
Individual counselling [16]			
Vs. minimal behaviour intervention	17	>6,000	1.56 (1.32 – 1.84)
Group counselling [17]			
Vs. self-help	16	>4,000	2.04 (1.60 – 2.60)
Vs. no intervention	7	815	2.17 (1.37 – 3.45)
Proactive Telephone counselling [18]			
Vs. less intensive interventions	13	>16,000	1.56 (1.38 – 1.77)
Self-help [19]			
Vs. no intervention	11	>13,000	1.24 (1.07 – 1.45)

Pharmacotherapy for tobacco dependence

Nicotine replacement therapies (NRTs) assist smokers in quitting by replacing nicotine that would otherwise be smoked, thereby reducing the need to smoke to obtain nicotine [52]. Nicotine replacement therapy is available in many forms. Nicotine replacement gum, lozenges, sublingual tablets, inhalers and nasal spray deliver nicotine through the oral or nasal mucosa. Nicotine replacement patches, which deliver nicotine through the skin, provide a passive, longer acting system of delivery [53, 54]. A Cochrane systematic review of the NRT literature found that all types of NRT significantly increase the odds of quitting with little difference between methods [52].

Antidepressant therapies, specifically bupropion SR and nortriptyline, are also used to help smokers quit. The antidepressant bupropion SR is the more widely used and studied agent [53, 55]. Nortriptyline has not been as widely studied and has not been approved for smoking cessation [55].

Nicotine replacement therapy (NRT)

Nicotine replacement therapies assist smokers in quitting by replacing nicotine that would otherwise be smoked, thereby reducing the need to smoke to obtain nicotine [56]. NRT is available in many forms. Nicotine replacement gum, lozenges, sublingual tablets, inhalers and nasal spray deliver nicotine through the oral or nasal mucosa.

The consistent use of one of these products doubles a person's odds of quitting smoking. However, NRT does not "make" you stop smoking. Behaviour change and support are essential. A smoking cessation program can take many forms, including self-help booklets and telephone counselling. In general, the more intense the behaviour modification therapy, the greater the chance of success.

Nicotine is the addictive substance in tobacco products. NRT provides nicotine so the body doesn't have to endure nicotine withdrawal while a person adapts to not smoking. Trying to learn skills to help in quitting smoking while dealing with nicotine withdrawal makes it harder to successful quit.

Nicotine withdrawal symptoms include irritability, difficulty concentrating, feelings of depression, difficulty sleeping, increased appetite cravings and headache. These symptoms often start just a few hours after the last cigarette. The first 72 hours of quitting are the hardest, but symptoms may persist for weeks. Smokers have learned that a cigarette will relieve these symptoms in a few moments. But taking nicotine in another form can suppress withdrawal. The NRT products only provide nicotine. They contain none of the carcinogens or toxic substances found in cigarette smoke.

No individual NRT currently available when administered as indicated matches the intensity and pattern of nicotine delivery of a cigarette, which delivers high levels of nicotine within minutes of smoking that gradually taper down over time. A slow delivery system, such as that of the nicotine patch, provides a more constant concentration of nicotine in the plasma to relieve cravings and tobacco withdrawal symptoms over time, whereas delivery methods that are faster acting, such as nasal spray or gum, can be used on demand for immediate relief of breakthrough cravings (Figure 1.) [57].

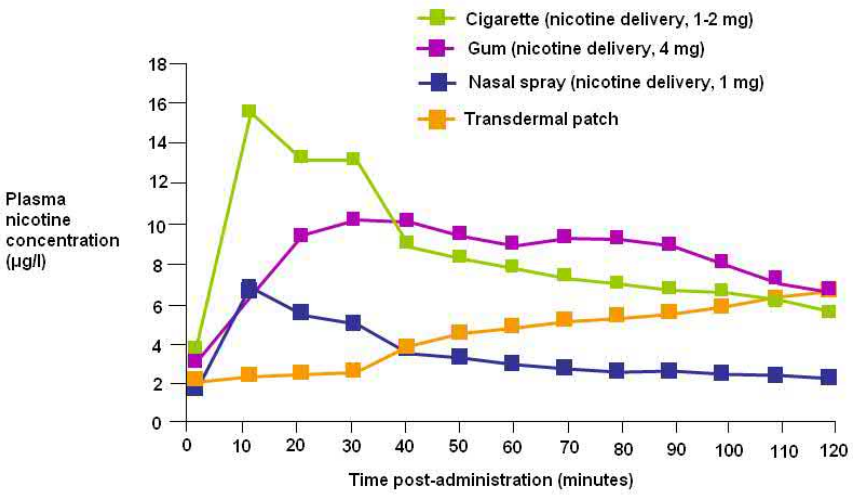


Figure 1. Nicotine delivery by cigarettes and NRT products [26]

A Cochrane systematic review of the NRT literature found that all types of NRT significantly increase the odds of quitting with little difference between methods. However, NRT efficacy compared with placebo remains suboptimal with an OR of 1.77, ranging from 1.66 for gum to 2.14 for the inhaler (Table 3.) [52, 53].

Table 3. Efficacy of Nicotine Replacement Therapy (NRT)

Comparison	N Trials	N Participants	Pooled OR (95% CI)
Gum	52	17,783	1.66 (1.52 – 1.81)
Patch	37	16,691	1.81 (1.63 – 2.02)
Nasal spray	4	887	2.35 (1.63 – 3.38)
Inhaler	4	976	2.14 (1.44 – 3.18)
Tablets/lozenges	4	2739	2.05 (1.62 – 2.59)
Combination vs. single type	7	3202	1.42 (1.14 – 1.76)
Any NRT vs. control	103	39,503	1.77 (1.66 – 1.88)

Bupropion SR

The recommended and maximum dose of bupropion SR is 300 mg/day, given as 150 mg twice daily. Dosing should begin at 150 mg/day given every day for the first 3 days, followed by a dose increase for most patients to the recommended usual dose of 300 mg/day. It is important that patients continue to receive counselling and support throughout treatment with bupropion SR, and for a period of time thereafter [58].

Comparison of nicotine replacement therapy (NRT) and bupropion SR therapy for quitting smoking

Only one head-to-head study has compared treatment with bupropion SR, the NRT patch, bupropion SR plus patch, and placebo [59, 60]. This double-blind, placebo-controlled trial randomized 244 patients to receive bupropion SR monotherapy, 244 to receive NRT patch monotherapy, 245 to receive both therapies, and 160 patients to placebo. Bupropion SR therapy was comprised of 150 mg per day for the first 3 days plus matching placebo, then 150 mg twice daily. Patients received 9 weeks of bupropion SR therapy and/or used the patch for 8 weeks. The study excluded smokers with clinical depression [59].

The 1-year continuous abstinence rates were significantly higher in the groups that received bupropion SR (18.4%) or bupropion SR plus the patch (22.5%) compared with the group that used the patch alone (9.8%) and the placebo group (5.6%) (P <0.001). The trend was similar for 1 year 7-day point prevalence of abstinence, with 15.6% of the placebo group, 16.4% of the patch-alone group, 30.3% of the bupropion SR-alone group (P <0.001), and 35.5% of the group that received bupropion SR plus the patch still remaining abstinent from smoking (P ≤ 0.001 for the bupropion SR groups vs. patch alone and placebo). Although abstinence rates were higher with combination therapy, the difference was not significantly different from the rate for the bupropion SR monotherapy group (Figure 2.).

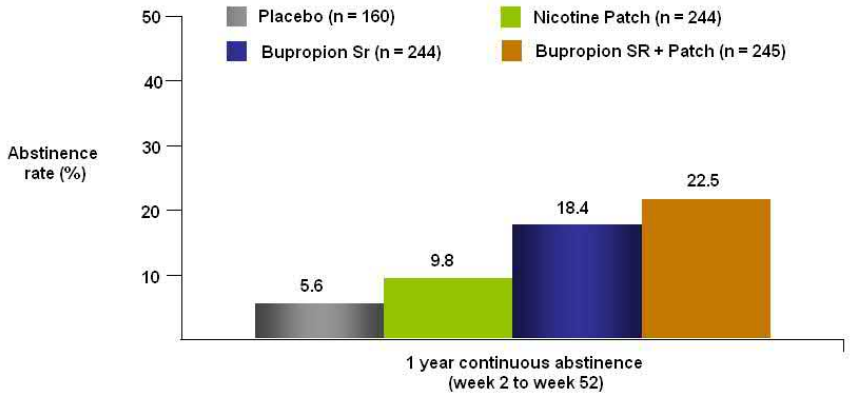


Figure 2. Comparison of nicotine replacement therapy (NRT) and bupropion SR therapy for quitting smoking

Varenicline: A highly selective α4β2 receptor partial agonist

Varenicline was deliberately designed for the α4β2 receptor, as a α4β2 nicotinic receptor partial agonist (with dual agonist and antagonist properties) and physically prevents nicotine from binding as an aid in smoking cessation.

The initial view of the mesolimbic system identifies the VTA where the α4β2 receptors predominate, as well as the nAcc. The release of dopamine at the nAcc from the axons of the dopamine cells of the VTA is believed to produce a reward response. When nicotine binds at the α4β2 nicotinic receptor in the VTA, it is believed to cause release of dopamine at the nAcc. Varenicline was deliberately designed for the α4β2 receptor, as an α4β2 nicotinic receptor partial agonist (with dual agonist and antagonist properties) and physically prevents nicotine from binding and releases intrinsically less dopamine at the nAcc (Figure 4.) [61, 62].

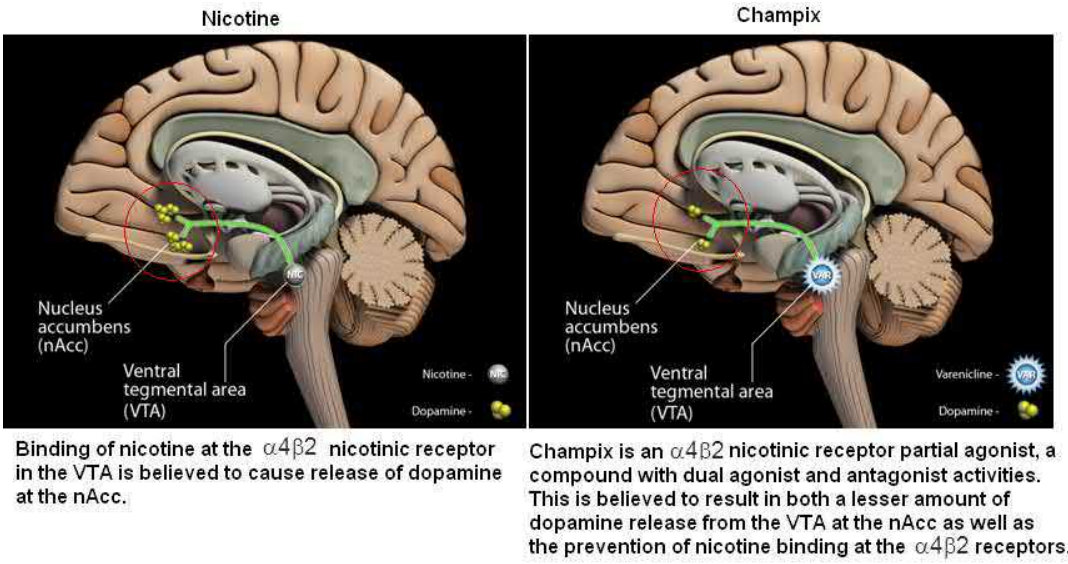


Figure 4. Varenicline

Varenicline mechanism of action: Efficacy for tobacco dependence

The efficacy of varenicline in smoking cessation results from its partial agonist activity at the α4β2 nicotinic receptor. By physically blocking the binding of nicotine, varenicline's partial agonist activity produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity) while simultaneously resulting in rewarding and reinforcing of the effects of smoking (antagonist activity) [63].

In summary, physicians can help smokers quit. Some smokers may need more help or multiple attempts. Success rates may be improved by using both non-pharmacologic and pharmacologic interventions. Varenicline is an innovative new class of treatment to help your patients reach their goal of long-term abstinence.

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The prevention of low-back pain and the possibilities of rehabilitation
Vilmos Dani MD

Back pain is among the most common complaints. Around 80% of the population suffer at least one episode of low-back pain in their lifetime.

What can be done to reduce the number of these complaints?

The physician's task

Children must be continuously screened for static disorders (such as flat feet) and anatomical abnormalities (like scoliosis, Scheuermann's disease, etc.) to ensure early recognition and treatment of these problems.

The most important task

- To ensure the healthy physical development of children and young people.
- To develop and strengthen the musculature of the trunk and to increase the flexibility and endurance of the body.

How can we do this?

We have to increase the level of physical activity of the whole population by encouraging regular, supervised participation in sport and other physical activities.

Special task of sports physician

Special attention must be paid in the case of sports that involve asymmetrical loading like tennis, fencing, canoeing, etc.

Prevention/therapy

- Regular conditioning exercises
- Focusing on symmetrical upper and lower back exercises
- Regular swimming
- Secondary sports
- Stretching exercises

Comprehensive back pain rehabilitation

- Medication using pills, injections and if necessary infusions
- Physiotherapy (ultrasound, iontophoresis, etc.)
- Massage
- Balneotherapy
- Supervised therapeutic gymnastics
- Psychological guidance

Supervised therapeutic gymnastics

- Physical activity must begin as soon as possible.
- The process of mastering the exercises must be supervised by a physician and it must be directed by an experienced, qualified physiotherapist
- Exercise must be done: carefully, gradually (with regard to both intensity and the number of repetitions), and regularly

Final message

- Screening and early recognition and treatment of static disorders and anatomical abnormalities!
- Encouragement of regular physical activity and sport among young people!
- The level of physical activity of the whole population must be increased!
- In comprehensive back pain rehabilitation supervised, regular and gradual therapeutic gymnastics and balneotherapy are very important!

The prevention and rehabilitation of sports injuries

Vilmos Dani MD

1. Is there any difference between the injuries suffered by sportsmen and those of the average person? No, there isn't.
2. Are there any differences between the stages of prevention and rehabilitation for athletes and for the average patient? Yes, there are: in the intensity of the exercises and the duration of the healing process

We can reduce the risk of injuries by paying attention to the following

The better your physical condition, the lower the risk of injury. Perform a complete warm-up before each practice or match and a cool-down afterwards, for approximately 10 to 15 minutes each. Pay attention to the correct performance of stretching exercises. After a strenuous practice or match a massage may help to relax the muscles.

Regular physical activity is essential. Improve your physical condition with regular running, jogging, cycling, swimming, etc.

The effects of regular exercise

- Strengthens the muscles, including the heart muscle
- Improves the circulation
- Increases the supply of blood and oxygen to the muscles and brain
- Increases stamina
- Improves the ability to concentrate
- Reduces the frequency of injuries
- Delays the onset of heart and circulatory diseases, diabetes mellitus, hypertension, osteoporosis, degeneration of bones and joints
- Helps to reduce excess weight

Warm-up

It is very important to prepare the body for intensive physical effort. Ensure a gradual build-up of training, so the body can get used to the extra load.

- Step 1. Running
- Step 2. General gymnastics

Stretching exercises

The cool-down and stretching exercises after sports activity both help in the regeneration of the body.

Massage

Massage helps to relax the muscles and increases blood flow to the tissues, which reduces muscle cramp and enhances recovery.

The most common injuries (among tennis players)

- Tennis elbow
- Achilles tendon injury
- Calf muscle strain („Tennis leg")
- Ankle sprain

The steps and exercises needed for prevention and rehabilitation of these injuries are similar.

Tennis elbow

Tennis elbow is the best-known and also the most painful injury in tennis players. It is an overuse injury of the extensor muscles of the wrist.

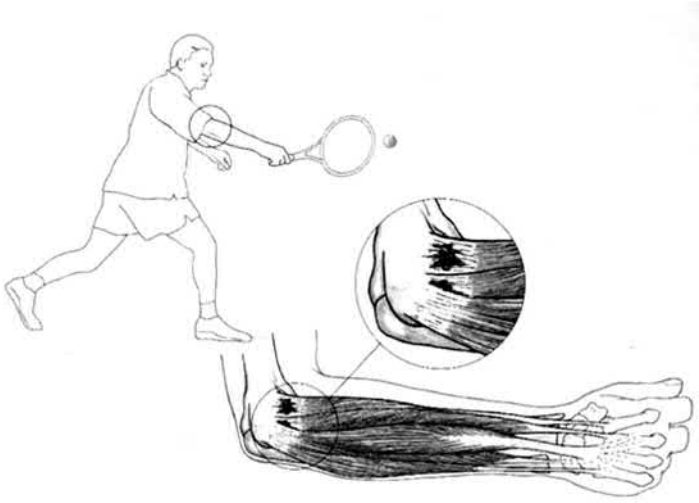

Figure 1. Tennis elbow

The pain is felt at the outer side of the elbow and it may radiate into the arm, wrist and fingers. Lifting, gripping, twisting the wrist, shaking hands, washing dishes or opening a door may all be very painful.

How can we prevent the injury? How can we ensure the best recovery?

We have to focus on improving flexibility and strengthening the forearm muscles. Stretch the forearm extensor muscles daily. Increase grip strength. Strengthen the forearm flexor muscles. Strengthen the forearm extensor muscles.

Achilles tendon injury

An injury of the Achilles tendon is a degenerative condition of the tendon, not an inflammatory process. It is a tendinopathy. The pain is felt in the Achilles tendon, 5-7 cm above the heel.

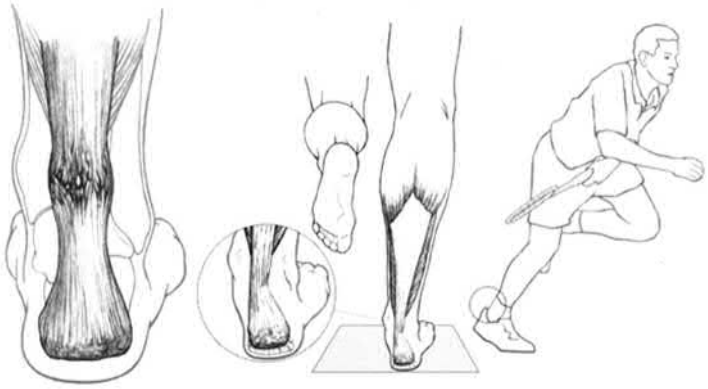

Figure 2. Achilles tendon injury

Calf muscle strain („Tennis leg")

„Tennis leg" is an incomplete rupture of the inside of the calf muscle. It is a typical tennis injury. The main symptom is a sudden, sharp or burning pain in the leg.

Figure 3. Calf muscle strain

Achilles tendon injury and calf muscle strain: How can we prevent the injury? How can we ensure the best recovery?

Cycle or swim for 20-30 minutes every day to preserve general fitness. It increases the blood flow to the calf muscles and enhances recovery. Stretch the short and long calf muscles. Stretch the short calf muscles. Strengthen the calf muscles. Do easy jogging, and easy running and jumping exercises.

General rule: Do not increase the intensity, frequency and duration of the practice too quickly.

Ankle sprain

A sprained or twisted ankle is one of the most common tennis (sport) injuries. In most cases, the injury is caused by landing on the outside of the foot. The relatively weak lateral ankle ligaments are then injured. The symptoms are pain and swelling around the ankle, mainly on the outside, later followed by discoloration of the skin.

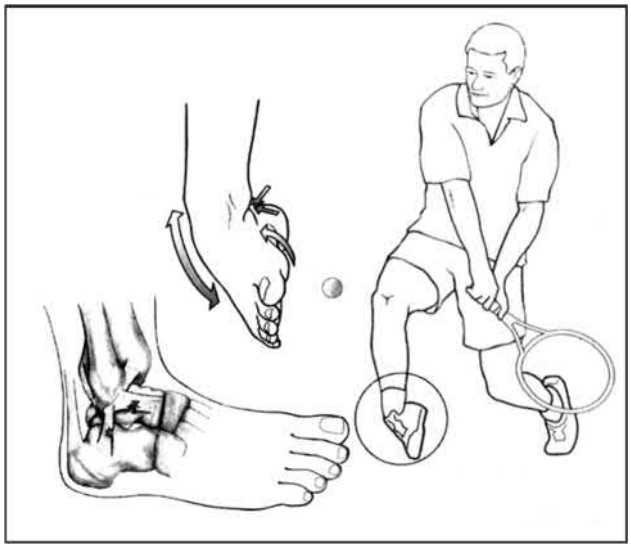

Figure 4. Ankle sprain

How can we prevent the injury? How can we ensure the best recovery?

Move the ankle without load. Walk on your heels, then on your toes. Finally walk on the inside of your feet and then on the outside of your feet. Stand on the injured foot, with arms spread to keep your balance. A very good exercise for the muscles around the ankle and foot is skipping. This should be done with care, however. It is important to build up this exercise gradually.

Conclusions

- The better your physical condition, the lower the risk of injury.
- Perform a complete warm-up before each practice or match, and a cool-down afterwards.
- Ensure a gradual build-up of training, so the body can get used to the extra load.
- Pay attention to the correct performance of stretching exercises.

Complementary and Alternative Medicine (CAM)
Ajándék Előry MD, PhD

Definition

According to the National Center for Complementary and Integrative Health (NCCIH) of the NIH, the term complementary and alternative medicine covers health care approaches developed outside of mainstream Western (conventional) medicine. When patients use these modalities together with conventional therapies, they are considered "complementary". When patients use them in place of Western medicine, they are "alternative" treatments. [1]. However, a transition can be seen in conventional biomedicine to an expanded, integrative medical model, which is more patient centred. This model incorporates multiple therapeutic approaches (old and new) to offer a greater choice for the patients and believes that the complexity of our biology cannot be understood from isolated parts [2].

CAM use

According to the results of the pan-European research network for CAM (CAMbrella.eu), the five most commonly therapies used by EU citizens are herbal medicine, homeopathy, chiropractic, acupuncture and reflexology [3].

Therapy	Prevalence across countries
Herbal Medicine	5.9 - 48.3%
Homeopathy	2 - 27%
Chiropractic	0.4 - 28.8%
Acupuncture	0.44 - 23%
Reflexology	0.4 - 21%

Conditions for which CAM is used

The most reported condition in CAM use was musculoskeletal problems, followed by respiratory problems. Back pain, urinary tract infection, ENT, allergy and psychological/mental/psychiatric problems were also prevalent. Preventative aims and smoking cessation were mentioned as well [3].

Reasons why people use CAM

"The main reasons were reported to be dissatisfaction or disappointment with a medical doctor or western medicine or that the doctor didn't understand or didn't take time or didn't seem interested in the problem.

Not wanting to take medical drugs, not wanting the side effects of drugs or invasive treatments and preferring natural methods were also mentioned as was having a better therapeutic relationship with a CAM practitioner, receiving a more personal service, on the advice of a friend or relative or to maintain health/general wellbeing." [3]

CAM categories according to the NCCIH

In recent years the grouping of complementary health approaches has become simpler. Currently the NCCIH classifies most of these modalities as

- natural products

- mind and body practices
- other complementary health approaches

Natural products

Herbs, vitamins and minerals fall into the group of natural products. They are widely used worldwide and especially important because they may interact conventional drugs. A practical guide for both the public and for healthcare professionals is the “About Herbs, Botanicals and Other Products” database of the Memorial Sloan-Kettering Cancer Center. This is an online, continuously updated database, which provides evidence-based information on a product’s traditional and proven uses, potential benefits, possible adverse effects and interactions with other herbs or medicines. (link: https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs)

Mind and body practices

The term mind and body practices comprise the techniques that enhance the mind’s interactions with bodily functions to induce relaxation and to improve overall health and well-being. Yoga, chiropractic and osteopathic manipulation, meditation and massage therapy are most widespread modalities of mind and body practices in the United States according to the NCCIH.

Other complementary health approaches

This category covers traditional Chinese medicine, Ayurvedic medicine, traditional healers, homeopathy and naturopathy.

The scientific evidence-base is the root of curing diseases in conventional Western medicine. However, scientific research on the different CAM modalities often conclude that they are ineffective, or the results are inconclusive. The Hungarian Academy of Science in its 2004 resolution rendered traditional Chinese medicine, manualtherapy/chiropractic/osteopathy and neuraltherapy evidence based [4]. Therefore, these three modalities will be discussed below in greater length.

Traditional Chinese Medicine

Diagnostic and therapeutic system based on complex theories: acupuncture, herbal medicines, massage (tui-na), physical exercise (tai-chi), diet are the main therapeutic components.

Acupuncture

- Insertion of needles into the skin and underlying tissues at acupuncture points
- Special diagnostic methods
- Prevention and therapy

EBM

- Evidence: several indications (nausea, vomiting, neck pain, osteoarthritis of the knee, back pain, dental pain) are supported by good evidence

Risks:

- Contraindications: severe bleeding disorders (needle acupuncture), first trimester of pregnancy, epilepsy
- Precautions/warnings: asepsis is mandatory, electro-acupuncture for patients with pacemakers, children
- Adverse effects: drowsiness, bleeding, bruising, pain during needle insertion, aggravation of presenting symptom, pneumothorax, infections

- Interaction: cardiac pacemaker

Tai chi

A system of movements and postures used to enhance mental and physical health

EBM

- Seems helpful in rheumatoid arthritis, hypertension, physical performance of the elderly

Risks:

- Contraindications: based on common sense (e.g. severe osteoporosis, severe heart conditions, acute back pain, knee problems, sprains and fractures)
- Usually it can be safely practiced during pregnancy and lactation
- Precautions/warnings: before starting tai chi older individuals should be carefully examined for any of the above or other contraindications.
- Adverse effects: rare, but may include delayed-onset muscle soreness, pulled ligaments or ankle sprains

Chinese herbal medicine

The medicinal use of preparation that contain plant, mineral or animal material

Risks:

- Preparations may have powerful pharmacological effects - risk of adverse effects is greater than most other complementary therapies.
- Interactions: different herbal preparations, conventional drugs
- Patients should be asked about self-prescription drug use

Massage

- Soft tissue manipulation of whole body areas
- Forms: refreshing massage, meridian massage (tui-na), Chinese point massage (acupressure), Qi massage
- Manual techniques: pressure, traction

Effects:

- Blood and lymph circulation is enhanced – increased oxygen supply
- Increased muscular tension can be affected beneficially

EBM

Beneficial in anxiety.

Likely to be beneficial: constipation, depression, labour pain, back pain, musculoskeletal pain

Risks:

- Contraindications: phlebitis, deep vein thrombosis, burns, skin infections, eczema, open wounds, bone fractures, advanced osteoporosis
- Precautions/warnings: cancer, myocardial infarction, osteoporosis, pregnancy
- Adverse effects: rare: bone fractures, liver rupture
- Interactions: possible with oil used for massage

Manipulated and body-based methods

Based on manipulation and/or movement of one or more parts of the body.

Chiropractic manipulation, osteopathic manipulation, massage

Chiropractic

- Subluxation of the vertebrae affects human health
- Chiropractors frequently use vertebral manipulation
- Treat mainly musculoskeletal problems

EBM

- Back pain - probably effective, not superior to exercise therapy.
- Serious risks exist especially with cervical manipulation.
- Risk-benefit balance marginally positive for back pain, for all other condition it is not.

Risks:

- Contraindications: osteoporosis, bleeding disorders, inflammatory or malignant diseases of the spine
- Precautions/warnings: patients with arteriosclerotic diseases of vertebral arteries
- Adverse effects: 50% - mild adverse effects. Cervical manipulation - stroke, arterial dissection
- Interactions: none known

Osteopathy

- Manual therapy: soft tissue manipulation, joint manipulation/mobilization
- Restore misalignment to optimize blood and lymph flow and organ functions
- Less forceful than chiropractic

EBM

- Effectiveness: Likely to be effective in acute/subacute back pain and shoulder pain

Risks:

- Contraindications: osteoporosis, neoplasms and infections of the bones, bleeding disorders
- Adverse effects: vertebral artery dissection
- Precautions and interactions are not known

Neural therapy

A treatment developed in Germany in the early twentieth century. It involves the injection of local anaesthetics into specific areas, often into old scars with the aim to resolve chronic longstanding illness or pain.

EBM:

- There isn’t enough data available to prove its effectiveness for back pain.
- Preliminary data show a reduction of subjective symptoms in multiple sclerosis.

Risks:

- Contraindications: allergic reactions to local anaesthetic, genetic illnesses and psychiatric illnesses other than depression.

- Adverse effects: allergic reactions, bleeding, infection, vasovagal reaction. Depending on the site of infiltration pneumothorax might occur, or device interference with pacemaker.
- Interactions depend on local anaesthetic employed.
- Precautions: needle phobia.

Placebo effect and new terms expressing it more accurately in complex interventions

Placebo

Inactive substance designed to satisfy (please) the patient. It has no intrinsic therapeutic value, does not contain the active ingredient, equivalent in all respects to the intrinsic therapeutic action but inert.

Efficacy: the evaluation of how successful a therapy is comparing to the placebo

Meaning response/context effect

Meaning response: physiological/psychological effects of meaning in the origins or treatment of illness [10]

Intervention associated expectations, intentions, understandings, or values of the patient and provider

Research background of context effect and meaning response

Neurophysiological research

Patient expectations modify the biological processes underlying pain perception in the brain [11].

Epidemiological research

Expectations on a positive outcome, optimism and support have long-term impact on hard clinical end points independently of other predictors [12].

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