
TECHNOLOGY ASSESSMENT REPORTS

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Treatment of Asthma and COPD: An Evidence-based Review

Somewhat over 1 million people in Sweden suffer from asthma or chronic obstructive pulmonary disease (COPD). These two diseases greatly reduce the quality of life, and together they account for approximately 2,300 deaths annually in Sweden.

ASTHMA

Asthma is a chronic inflammatory disease of the bronchial airways that leads to periods of reduced airflow and respiratory distress. The disease, particularly allergic asthma, has increased in Sweden and other western countries in recent decades. The increase is most notable among children and adolescents. Approximately 6% to 8% of all Swedish schoolchildren are estimated to have asthma. The disease is equally common among adults. Approximately 700,000 people in Sweden suffer from asthma. Hospital admissions due to asthma have, nevertheless, declined by two-thirds since 1987. Somewhat over 250 people died from asthma in 1997.

The basic reasons why certain individuals develop asthma and why asthma is increasing remain unknown despite intensive research. There is a strong association between asthma and respiratory tract allergies, e.g., to cats or dust mites. Common symptoms are sudden respiratory distress—particularly in cold air, during respiratory tract infections, and during stress—“wheezy chest,” and nocturnal coughing. Most people are free of symptoms between the attacks, but are always at greater risk for a new attack when any of the triggering factors is present. Some people are affected by repeated severe asthma attacks that can be life-threatening. With the help of new medications, many people with asthma can now live nearly normal lives, and hospital admissions and mortality due to asthma have become uncommon. Having a chronic disease such as asthma, however, still places a major burden on the individual—both in school, at work, and during recreational time and on the family.

COPD

The dominant cause of COPD is tobacco smoking. While asthma has been known for thousands of years, COPD represents a new disease concept. Airway obstructions, i.e.,

reduced airflow in the respiratory tract, is common to the obstructive respiratory diseases of asthma and COPD. In asthma, pulmonary function usually returns to normal between attacks. In COPD, however, the airway obstruction is chronic and leads to a progressive reduction in breathing ability. The concept of COPD includes long-term coughing with increased mucus production (chronic bronchitis) and destruction of the smallest airways and the pulmonary alveoli (emphysema).

The continual respiratory distress in advanced COPD creates anxiety, substantially reduces the quality of life, and often leads to social isolation for the patient. The association with smoking causes many to perceive the disease as self-induced and a social stigma. Acute deteriorations that lead to emergency room visits and hospital admissions are common. In males with COPD, the number of hospital admissions has remained unchanged over the past decade, but has doubled for women.

Late stages of the disease are accompanied by reduced oxygenation and respiratory failure, which often leads to death. Since the late 1980s, mortality has nearly doubled. The number of women who die due to COPD has increased and reached 800 in 1997. The same year, 1,250 men died due to COPD.

The gradual increase of the disease in Sweden reflects smoking habits following World War II, when smoking became a serious problem among women. When the disease appears—often as chronic “smoker’s cough” and severe shortness of breath, usually after 30 to 50 years of smoking—patients with COPD have already lost half or more of their breathing capacity. Earlier it was thought that only a minority of smokers were affected by COPD, but recent Swedish studies show that in smokers who reach higher ages, nearly one-half develops COPD. From 50 years of age and upward, approximately 8% of the population has COPD, corresponding to 400,000 Swedish people. Only about 40% of these are known by diagnosis. Despite the major suffering involved in COPD for those affected, and despite the rapidly increasing cost of hospitalization, primary care visits, and drugs, the disease has not received major attention.

SOCIOECONOMIC COSTS OF ASTHMA AND COPD

In 1991, the direct healthcare costs for asthma and COPD in Sweden were nearly equal, each costing approximately SEK 1.1 billion per year. Added were the indirect costs, i.e., production loss due to sick leave, early retirement, and premature death, at an annual cost of SEK 1.9 billion for asthma and SEK 1.7 billion for COPD. Thus, the total socioeconomic costs for asthma and COPD totaled approximately SEK 6 billion.

Currently (year 2000), the total socioeconomic costs for asthma and COPD are approximately SEK 7 billion. The costs for drugs and outpatient services have increased for both asthma and COPD since 1991, while the costs for inpatient short-term acute hospital care have declined for asthma but increased for COPD.

AIM

The aim of this study is to systematically and critically review the scientific base for the various types of treatment for asthma (both in children and adults) and COPD. Assessment of primary prevention is not included. The cost-effectiveness of treatment is addressed.

METHODS

Selecting Outcome Measures

Opinions vary on how to best assess the effects of different treatments for asthma and COPD. Traditionally, various physiological pulmonary measurements of airflow or breathing capacity have dominated as outcome measures in treatment research in this field. The

basis for this reasoning has been that if a treatment improves airflow in the lungs it must benefit the patient. It has taken many years to gain acceptance for the idea that the purpose of treatment is not limited to improving airflow. Patients do not suffer from the reduced airflow, but from its impact on daily life, e.g., the breathing distress and anxiety that accompanies reduced pulmonary function or the periods of deterioration that require acute care. Impaired pulmonary function is, however, not unimportant for patients with asthma or COPD, but there is a weak association between pulmonary function and how patients experience their disease and its impact.

The following four primary outcome measures, which are important for individuals with asthma or COPD, have been used in the report (not in rank order):

- Mortality from asthma or COPD;
- Need for increased medication, emergency visits, or hospital admission;
- Health-related quality of life; and
- Symptoms.

Literature Search and Review

This report is based on a systematic and critical analysis of results from studies that have been published in the international scientific literature. During the course of the project, the Cochrane Collaboration has also published several reviews in this field, some of which are included in the report. The literature search in MEDLINE and other databases includes studies published through June 1999, with inclusion of some later studies.

For inclusion in this review, the studies must be of high quality, i.e., they should:

- Be randomized and controlled or be a quality-controlled, systematic review of such studies;
- Report on at least one of the four primary outcome measures; and
- Use a treatment period of at least 3 months.

Using the above criteria, many studies were excluded from the review. No documentation of high quality could be found in some therapeutic areas. In such cases, the review included studies which did not report on any of the primary outcome measures, used shorter treatment times, or had other deficiencies in study design. Such studies are of lower quality and provide a weak basis for conclusions. Studies of treatment for acute exacerbation have been included in the review, although only data for pulmonary function were included and followup times were short. As regards drug studies, only studies that included drugs approved in Sweden were reviewed. In the treatment studies for asthma, the gender distribution among patients is similar while the COPD studies are highly dominated by men. Gender-specific analyses of treatment results are almost completely lacking.

Synthesis and Grading Conclusions

Approximately 350 studies met the basic standards for scientific quality. These studies were reviewed, assessed, and considered as a basis for conclusions according to the following four-grade scale:

- Grade 1 – Strong support (for conclusions);
- Grade 2 – Moderate support;
- Grade 3 – Weak support; and
- Grade 4 – Little support, including consensus among experts or no support.

Although the grading of conclusions cannot be interpreted as the absolute truth, Grade 1 conclusions should provide more concrete evidence than Grade 3 or Grade 4. It is important to note that a conclusion at Grade 4 does not necessarily mean that a particular treatment is ineffective. It only means that the scientific basis for assessment is insufficient. On the other hand, conclusions concerning the lack of effects may be ranked as Grade 1, 2, or 3.

RESULTS OF THE LITERATURE REVIEW

Preventive Interventions

Since the reasons underlying why some people develop asthma are yet unknown, there is no effective primary prevention. Many attempts to stop the development of asthma by intervening on known or suspected risk factors, mainly allergies, have been carried out, but without convincing results. A review of primary prevention is, however, beyond the scope of the group's work.

The most important interventions in the primary prevention of COPD are to prevent the debut of smoking and to facilitate smoking cessation. Unfortunately, we do not have effective strategies for achieving these goals. An SBU report on smoking cessation in 1998 described the state of current knowledge. The report also emphasized the importance of brief counseling when smokers come into contact with the health and dental services, and that the use of nicotine replacement agents increases the percentage who successfully stop smoking.

Measures for preventing or reducing symptoms or deterioration of the disease (secondary prevention) in those who already have asthma or COPD have been assessed to a surprisingly small extent. For decades, individuals with allergic asthma have received advice to reduce their exposure to allergens, e.g., those allergic to cats should not own cats. The effects of such advice are inadequately assessed. Only as regards anti-mite interventions is there documentation that this measure reduces the onset of asthma symptoms in mite-allergic individuals with asthma (Grade 3). The effectiveness of using air cleaners for asthma has not been demonstrated (Grade 1).

Middle-aged individuals with moderate or severe COPD who stop smoking live on average 7 years longer than those who continue to smoke (Grade 3). Smokers with COPD who successfully stop smoking substantially reduce coughing and mucus formation, while wheezing and shortness of breath decline to a lesser extent (Grade 1). Notably, there is a lack of evidence to show whether smoking cessation leads to recovery from asthma or a reduction in asthma symptoms (Grade 4).

Physical Training and Patient Education

Asthma and COPD are common chronic diseases. Hence, a range of educational and rehabilitation programs have been developed for patients with these disorders. Asthma schools and COPD schools have become commonplace, and physical training has taken a prominent place in treating COPD in Sweden. Most of the reviewed studies address both education and training as concurrent interventions, and hence they are presented together in the report. The report concluded that self-care programs for asthmatic adults may have favorable effects on symptoms and care needs (Grade 1), while general information alone has no proven effect in children and adults with asthma (Grade 1).

However, it is noteworthy that the evidence is insufficient for judging the effects of self-care programs for asthma in Swedish environments (Grade 4) even though asthma schools and similar programs are recommended by many local clinical guidelines. Rehabilitation that includes physical training offers good effects on the quality of life, shortness of breath, and functional work capacity in patients with moderate COPD (Grade 2). However, it is

unclear whether patients with advanced COPD have equally great benefits from physical exercise (Grade 4). Structured activities at community health centers (so-called asthma clinics) for patients with asthma may have some favorable effects on symptoms, emergency visits, and sick leave, but the scientific evidence is deficient (Grade 4).

Alternative Therapies

Outside the publicly financed health services, many alternative methods for treating disease are used by professional practitioners and in self-care. The borderline between conventional medical therapy and alternative medicine or complementary methods is not clearly delineated. Consequently, acupuncture, e.g., is used by some physicians and physiotherapists. Given the background of increasing interest in Sweden for alternative medical therapies, the working group committed substantial effort toward reviewing the alternative methods used to treat asthma and COPD. We found very few studies that met our requirements, despite our own extensive search of the literature and the use of systematic reviews by the Cochrane Collaboration. The only area where it was possible to draw reliable conclusions concerned nutritional therapy. The first is that supplements of unsaturated fatty acids (fish oil) have no effects in treating asthma (Grade 1). The second is that energy supplements in the diet for patients with COPD can increase the sense of wellbeing and reduce the degree of respiratory distress (Grade 3).

Most of the studies reviewed had short duration of treatment, small and incompletely described patient data, or other deficiencies in trial design. Hence, evidence upon which to base conclusions on treatment effects is deficient or completely lacking (Grade 4). This applies to the following treatments: climate therapy, psychological treatment including family therapy, hypnosis and behavioral therapy, acupuncture, homeopathy, chiropractic, yoga, reflexology, massage, qi gong, relaxation, and biofeedback.

PHARMACOLOGIC TREATMENT

Beta-2 Stimulants and Anticholinergics

Bronchodilating agents have traditionally been used to treat acute asthma attacks. Ephedrine from the leaves of the ephedra plant and “asthma cigarettes” produced from the leaves of the thorn apple were even used in Sweden well into the 1900s. Adrenaline for acute treatment was introduced around 1900. The selective beta-2 stimulants, which we continue to use widely, were introduced in the 1960s and complemented in the 1990s by long-acting beta-2 stimulants. “Asthma cigarettes” were replaced in the 1970s by a pure anticholinergic that continues to be used in treating asthma and COPD. A characteristic common to beta-2 stimulants and anticholinergics is that they mainly have a bronchodilator effect.

Acute Asthma. Adrenaline has no advantages over selective beta-2 stimulants in treating acute asthma and children and adults (Grade 2). Clinical experience suggests that acute treatment with selective beta-2 stimulants has favorable effects in adults – although placebo controlled studies are lacking (Grade 4) – and probably has effects in children (Grade 3). On the other hand, beta-2 stimulants have no, or only minor, effects in the treatment of acute obstructive conditions related to viral airway infections in children under 1 year of age, so-called bronchiolitis (Grade 2). Adding inhalant anticholinergics to beta-2 stimulants has a favorable effect in children (Grade 2) and reduces the need for hospitalization in treating adults (Grade 1).

Maintenance Therapy for Asthma. Continued maintenance therapy with a short-acting beta-2 stimulant as the only medication, or as a supplement to other therapy, does not improve asthma control in adults (Grade 2). However, the evidence is insufficient to determine the value of maintenance therapy in children (Grade 4). Long-acting beta-2

stimulants have effects in both children (Grade 3) and adults (Grade 1) as a supplement to inhaled steroids or other treatment. Evidence is lacking or deficient for determining the effects of maintenance therapy with inhaled anticholinergics in children and adults with asthma (Grade 4).

Acute Exacerbation in COPD. The evidence is deficient for judging the value of both beta-2 stimulants and anticholinergics for this indication, despite a treatment tradition that has lasted many years (Grade 4).

Maintenance Therapy for COPD. Long-acting beta-2-stimulants provide small improvements in symptoms and quality of life in maintenance therapy (Grade 1). Maintenance therapy with anticholinergics has effects on symptoms and quality of life (Grade 2), but does not reduce the need for hospitalization and does not influence mortality (Grade 3).

Theophylline

Xanthine derivatives such as caffeine have some bronchodilating effects on asthma. One such derivative, theophylline, was introduced in the 1930s and was used widely in Sweden until the 1980s, both in acute and maintenance treatment of asthma and to some extent for COPD. Since then, its use has progressively declined, due in part to its adverse side effects. The review shows that oral maintenance treatment with theophylline for asthma in adults has no favorable effects (Grade 1), while the evidence for determining the effects in children and in COPD is deficient (Grade 4). Given intravenously for acute asthma, theophylline has the same effects as inhalation of beta-2 stimulants, but unfavorable side effects (Grade 2). The drug has a supplementary effect in acute asthma when the effect of inhaled beta-2 stimulants is insufficient (Grade 2).

Glucocorticoids

Glucocorticoids in the form of cortisone (usually called steroids) were first used for asthma in the early 1950s and were quickly found to have dramatic effects on asthma when used in high oral doses. Severe side effects such as growth inhibition in children and osteoporosis in adults gave the treatment a bad reputation. Inhaled steroids were introduced in the early 1970s, and were established as first-line treatment for asthma in both children and adults during the 1990s, due in part to the increasing knowledge about the effects of steroids on the underlying inflammation of the bronchi in asthma.

Although COPD is an inflammatory bronchial disease, the inflammation is of a different character than in asthma. Hence, it is not surprising that the clinical effects of steroids on COPD are not as apparent. However, the scientific documentation is also more limited. Compared to oral administration, inhaled steroids have a clear advantage as regards the relation between effects and side effects. Therefore, the working group's review has focused on this type of medication. Based on comparative studies that have been published, the group did not find it meaningful to assess the possible differences among available inhaled steroids and their different delivery devices since the studies seldom meet the requirements that should be placed on such comparative studies.

The side effects of inhaled steroids are rare and often depend on dosage: hoarseness, increased risk for superficial bruising, and often a minor and temporary influence on height growth in children.

Asthma in Children over 2 Years of Age and in Adults. Maintenance therapy using inhaled steroids has important effects both in children and adults with asthma (Grade 1). In adults with severe asthma, inhaled steroids reduce the need for oral steroids (Grade 1) and reduce the risk for death from asthma (Grade 3). In maintenance therapy of children with mild asthma, inhaled steroids reduce the symptoms better than long-acting

beta-2 stimulants (Grade 3), and inhaled steroids reduce symptoms better than theophylline in adults with mild asthma (Grade 3). The addition of long-acting beta-2 stimulants to inhaled steroids provides better asthma control in both children (Grade 3) and adults (Grade 1). Unfortunately, there is no evidence for permanent treatment effects following discontinued treatment. Symptoms return after exposure, even after a longer period of treatment with inhaled steroids for mild asthma in both children and adults (Grade 2).

Short-term oral steroid regimens after treatment for acute asthma reduce the number of new asthma attacks that require treatment and the number of hospital admissions (Grade 1).

Treatment Effects in COPD. Long-term treatment with inhaled steroids does not prevent progressive deterioration of pulmonary function in COPD (Grade 1). In advanced COPD, inhaled steroids reduce the number of acute exacerbations (Grade 3). In episodes that require treatment, oral and intravenous steroids have minor, but clinically relevant, effects (Grade 2).

Cromoglycate

Cromoglycate is an antiinflammatory drug that has been used in Sweden since the early 1970s to treat asthma and allergic eye and nose problems. The drug has local effects only and no serious side effects. The review shows that cromoglycate has favorable effects mainly in mild to moderate asthma in children over 4 years of age and in adults (Grade 1). The effects of treatment in children are less pronounced than the effects of inhaled steroids (Grade 3), but data for comparisons in adults is lacking (Grade 4).

Antileukotrienes

Antileukotrienes, a new group of drugs for treating asthma were introduced in the late 1990s and have not yet secured a position in the treatment arsenal. To date, only one drug in the antileukotriene group has been registered in Sweden. This drug is delivered orally. Maintenance treatment with antileukotrienes reduces the frequency of attacks and the need for additional medication. It also improves quality of life in mild and moderate asthma cases in both adolescents and adults (Grade 1), but treatment in adults has a lesser effect than inhaled steroids in moderate doses (Grade 2). The evidence is insufficient concerning treatment of children (Grade 4).

Antihistamines

Since the 1950s, antihistamines have been used for effective treatment of nose, eye, and skin allergies. Our review concludes that the evidence is insufficient for determining their effects on asthma symptoms related to pollen allergies and on perennial asthma (Grade 4).

Cough Medicines

Coughing and expectoration are common, important, and often disturbing symptoms in both asthma and COPD, but also appear in many other diseases involving the bronchi and lungs. Regardless of the cause for coughing, treatment should be aimed at the basic cause and not at the symptoms. Traditionally, a large number of different decoctions and mixtures have been used to inhibit coughing (cough suppressants) or to promote expectoration. Modern documentation is lacking for all of these agents. Sales of cough medicine remain high in Sweden, particularly in self-care.

Evidence is lacking to assess the effects on coughing and expectoration in long-term treatment with cough medicines for asthma and COPD (Grade 4). Long-term treatment with acetylcysteine provides a small reduction in the number of acute episodes in patients with chronic bronchitis at various grades of COPD (Grade 1).

Immunosuppression

In some cases, patients with severe asthma may not achieve satisfactory asthma control through high doses of inhaled steroids in combination with other drugs. This often leads to repeated oral steroid treatment, in some cases even to continual steroid treatment. Adding drugs that inhibit immunological processes has been tested in such cases. The review shows that methotrexate can lead to a reduction in oral steroid doses for severe asthma, but the treatment also carries troublesome side effects (Grade 2). The evidence for cyclosporin is weaker (Grade 3).

Specific Immunotherapy with Allergen Extracts

Specific immunotherapy—or hyposensitization as it was formerly called – has been used since the early 1900s in persons with allergic hay fever and asthma. In the late 1970s, allergen extracts with standardized contents of allergens were introduced and gradually replaced earlier, unspecified extracts. The effects in allergic asthma have been questioned from time to time. Immunotherapy is given over a long period, usually 3 years, as injections in the skin. Serious acute side effects may appear. The review shows that immunotherapy has favorable effects on allergy-triggered asthma symptoms (Grade 1). The effects are best documented for pollen and cat allergies (Grade 1), less well documented for mite allergies (Grade 3), and the evidence is lacking as regards dog allergies (Grade 4).

Antibiotic Treatment for Acute Exacerbations in Chronic Bronchitis

Patients with chronic bronchitis, with or without COPD, are often afflicted with respiratory tract infections and acute exacerbations. Some, but not all, of these episodes are caused by bacteria. Placebo-controlled studies suggest that treatment with tetracyclines, amoxicillin, and trimethoprim-sulfamethoxazole of patients with chronic bronchitis, with or without COPD, shortens the exacerbation and reduces symptoms (Grade 2).

Oxygen Therapy at Home

Oxygen deficiency may appear in case of severe COPD. In the beginning, it may occur only during acute exacerbations, but later it may become chronic. Chronic oxygen deficiency substantially reduces survival. Chronic oxygen deficiency can be treated with well-controlled, continual administration of oxygen. Treatment is technically rather complicated, relatively expensive, and requires that the patient can follow the instructions and does not smoke. Since 1987, Sweden keeps a national registry of patients on home oxygen therapy, which makes it possible to monitor the treatment strategies, survival, etc. The review led to the conclusions that continuous oxygen therapy extends survival in COPD patients with severe chronic oxygen deficiency (Grade 1), but it has no proven effect on mild or moderate daytime oxygen deficiency (Grade 2).

To facilitate oxygen therapy and improve the condition of patients with severe COPD, different home healthcare nursing models have been tested. Specific clinical guidelines, e.g., involving home visits by special nurses, have not shown any effects on quality of life or hospital admissions for patients with severe COPD (Grade 2).

Cardiovascular Drugs in COPD

In severe cases of COPD with chronic oxygen deficiency, some patients develop elevated pressure in the pulmonary circulatory system, resulting in edema. Traditionally, these patients have been treated with diuretics and, in some cases, digitalis. Vasodilators have been proposed as a treatment strategy for elevated pressure in pulmonary circulation. The review concludes that vasodilating agents have no effect on survival in COPD (Grade 3).

Remarkably, the data are insufficient for assessing the almost routine use of diuretics in severe COPD (Grade 4).

Lung Surgery for Emphysema

Volume-reducing lung surgery as treatment in selected patients with severe COPD and emphysema was tested as early as the 1950s, but has been used on a wider scale since the early 1990s. Only a small percentage of these patients are candidates for surgery. The method has received major attention in the mass media because of patients in whom the initial effects were very good. However, the scientific evidence supporting the method is scant. Mortality in conjunction with surgery has been 0% to 6% in uncontrolled studies. Preliminary results from an ongoing Swedish controlled study suggest that health-related quality of life improves for at least 1.0 to 1.5 years following surgery (Grade 3).

Reflux Treatment

In addition to acid reflux and heartburn, regurgitation of acid stomach contents into the esophagus can also cause problems in the respiratory tract and exacerbate asthma, particularly at night. Asthma and reflux problems co-vary, and certain asthma drugs, e.g., theophylline, increase the tendency for reflux. Various studies have assessed the treatment of reflux using both drugs and surgery, but without confirmed effects on asthma symptoms (Grade 2).

Antioxidants

Epidemiologic and immunologic studies suggest that low levels of antioxidants in the blood, e.g., vitamins C, E, etc. may be associated with asthma. However, there is insufficient evidence to determine whether the administration of antioxidants has any effect in asthma (Grade 4).

CONCLUSIONS

- Asthma and COPD are both chronic public health diseases that are on the rise in Sweden. For asthma, the increase is most obvious among children and young adults, while COPD is increasing among older smokers, particularly women.
- The cause behind the increase in asthma is unknown. However, the dominant, confirmed cause behind COPD is tobacco smoking. To prevent the progression of COPD, it is important to detect the disease early. The most important preventive measure is to intervene effectively against smoking.
- COPD is associated with substantial limitations in everyday life and a reduced quality of life despite medication. Although asthma also leads to a impaired quality of life, individuals with asthma have a greater chance of becoming symptom-free through modern medication. To assess the treatment of asthma and COPD, it is essential to use outcome measures that reflect the impact of the disease on an individual's life (health-related quality of life, symptom scales, need for acute care, mortality).
- The new drugs for treating asthma have major advantages. They also have contributed toward a dramatic decline in the cost of hospitalization for asthma patients.
- The review of the scientific literature has shown:
 - That smoking cessation is the single most important intervention against COPD. Smoking cessation increases survival substantially and reduces symptoms. For many individuals with severe COPD, drugs provide only limited relief for their exposed medical, psychological, and social situation;
 - That current maintenance treatment for asthma using long-acting beta-2 stimulants and inhaled steroids is based on solid scientific evidence that shows a positive effect;
 - That treatment as needed with short-acting beta stimulants for asthma symptoms and exacerbations is well founded;

- That other treatment principles for asthma such as cromoglycate, antileukotrienes, and immunotherapy have documented effects;
- That the benefits of cough medications in obstructive lung diseases is inadequately studied;
- That treatment with theophylline tablets is not beneficial for patients;
- That continual treatment with short-acting beta stimulants is not effective;
- That preventive measures against asthma symptoms, such as allergen elimination, need to be assessed; and
- That scientific evidence on alternative (complementary) treatment methods for asthma and COPD is either weak or completely lacking. There is a major need for controlled, well-executed studies.
- Methods for improving patient compliance with treatment regimens need to be developed and can be strengthened when patients themselves participate in decisions on treatment methods.
- There is a major need to assess special asthma clinics and treatment methods at home for severe COPD. Different forms of COPD rehabilitation play an important role, but need to be developed and assessed.

APPENDIX 1

Overview of the Effects of Various Treatments for Asthma and COPD

An overview of current knowledge is presented in the following tables, which summarize the most important conclusions from the systematic review. Such tables are necessarily schematic and cannot fully represent the detailed reasoning underlying each of the 24 chapters. Hence, they must be complemented with the more detailed information presented in the summary and the text of the report.

The following symbols are used in the tables to indicate the effects of the methods:

(+) = favorable effects;

(0) = no proven favorable effects;

(?) = documentation lacking or deficient.

The evidence underlying each evaluation was graded to indicate the strength of the scientific evidence:

1 = strong support by scientific studies;

2 = moderate support;

3 = weak support;

4 = little or no support or consensus among experts (for areas not reviewed by modern scientific methods, e.g., treatment with theophylline or beta stimulants in acute asthma).

Asthma Treatment in Adults

Table 1. Effects of Treating Acute Asthma in Adults

Treatment	Effect	Evidence grade	Comments
Beta-2 stimulants	+	4	Regardless of medication type
Beta-2 stimulants, inhaled	+	1	Better than intravenous
Beta-2 stimulants + anticholinergics, inhaled	+	1	Fewer admission
Theophylline	+	4	More side effects than beta-2
Theophylline as complement to beta-2 stimulants	+	2	
Steroids	+	1	No advantage with parenteral administration

Table 2. Effects of Methods and Drugs in Maintenance Treatment of Asthma in Adults

Treatment	Effect	Evidence grade	Comments
Anti-mite measures	+	3	
Air filters	0	1	
Smoking cessation	?	4	
Education (information only)	0	1	
Physical training	?	4	
Self-care program	+	1	Swedish studies lacking
Asthma clinics in primary care	+	4	Insufficient evidence
Psychological treatment	?	4	
Alternative medicine methods	?	4	Deficient for acupuncture, homeopathy, and chiropractic. Lacking for others.
Unsaturated (omega 3) fatty acids	0	1	
Climate therapy	?	4	
Short-acting beta-2 stimulants in continual treatment	0	2	
Long-acting beta stimulants	+	1	
Anticholinergics	?	4	
Theophylline	0	1	Unfavorable side effects
Inhaled steroids			
— symptoms, exacerbations, and quality of life	+	1	
— survival	+	3	
Cromoglycate	+	1	Mild-moderate asthma
Antileukotrienes	+	1	Mild-moderate asthma
Antihistamines	?	4	
Cough medicines	?	4	
Immunosuppression			
— methotrexate	+	2	Less need for oral steroids
— cyclosporin	+	3	Less need for oral steroids
Specific immunotherapy for allergy-triggered asthma symptoms	+	1	Best for pollen and cat allergies (1), less certain for mite allergies (3), deficient evidence for dog allergies (4)
Treating reflux	0	2	
Antioxidants	?	4	

Table 3. Effects of Treating Acute Asthma in Children

Treatment	Effect	Evidence grade	Comments
Beta-2 stimulants	+	3	
Beta-2 stimulants+ anticholinergics	+	2	
Theophylline	+	4	No advantages compared to beta-2 in inhalation, but a supplementary effect (2)
Steroids	+	1	

Table 4. Effects of Methods and Drugs for Treatment of Asthma in Children

Treatment	Effect	Evidence grade	Comments
Anti-mite measures	+	3	
Air-filters	0	1	
Reduced smoking by parents	?	4	
Smoking cessation in adolescents	?	4	
Education (information only)	0	1	
Physical training	?	4	
Psychological therapy	?	4	
Short-acting beta-2 stimulants, continual treatment	?	4	
Long-acting beta-2 stimulants	+	3	
Anticholinergics	?	4	
Theophylline	?	4	
Inhaled steroids	+	1	Symptoms and exacerbations
Cromoglycate	+	1	Mild-moderate asthma over 4 years.
Antileukotrienes	+	1	Only shown in adolescents
Specific immunotherapy for allergy-triggered asthma symptoms	+	1	Best for pollen and cat allergies (1), less certain for mite-allergies (3), deficient for dog allergies (4)

Table 5. Effects of Treatment on Acute Exacerbation in COPD

Treatment	Effect	Evidence grade	Comments
Beta-2 stimulants	?	4	
Beta-2 stimulants+anticholinergics	?	4	
Theophylline	?	4	
Steroids	+	2	
Antibiotics	+	2	Amoxicillin, tetracycline, trimsulfa

Table 6. Effects of Methods and Drugs for Maintenance Treatment

Treatment	Effect	Evidence grade	Comments
Smoking cessation			
—survival	+	1	7-years longer survival
—symptoms	+	1	Best effects on coughing and mucous formation.
Rehabilitation by physical training			
—respiratory distress	+	1	
—quality of life	+	2	
Energy supplements	+	3	
Climate therapy	?	4	
Long-acting beta-2 stimulants	+	1	Small effects

(continued)

Table 6. (Continued)

Treatment	Effect	Evidence grade	Comments
Anticholinergics	+	2	Symptoms and quality of life
Theophylline	?	4	
Inhaled steroids	+	3	Only shown for the number of acute exacerbations
Antileukotrienes	?	4	Somewhat fewer acute exacerbations and sick days
Cough medicine	?	4	
Acetylcystein	+	2	
Oxygen-survival	+	1	In severe oxygen deficiency (PaO ₂ < 7.3)
Digitalis and diuretics	?	4	
Vasodilator drugs - survival	0	3	
Volume reducing surgery for emphysema			
- quality of life	+	3	
- survival in the longer perspective	?	4	
Antioxidants	?	4	

Hormone Replacement Therapy: An Evidence-based Review

Estrogen is a female sex hormone that has long been used to treat the symptoms of menopause. Estrogen is also used for preventive purposes to counteract the risks for cardiovascular disease and osteoporosis-related fractures.

The medical effects of estrogen treatment are known to some extent but much remains to be learned, particularly concerning long-term effects and risks. Using scientific methods to acquire precise knowledge about the risks and benefits of estrogen treatment is a complex endeavor, in part because treatment is not uniform. The types of agents, duration of treatment, dosage, and combinations with other hormones vary. Acquiring a comprehensive assessment of the entire field requires very large studies that can demonstrate the effects on total mortality.

Critical review of the scientific literature has identified many gaps in knowledge. A detailed accounting of these gaps appears in the chapters of this report. Clearly, further studies are needed within the broad area of hormone replacement therapy after menopause.

In 1996, SBU published a scientific review of estrogen treatment following menopause. Since then, several important studies have been published in the field. Hence, there was reason to review the recent scientific literature and determine the extent to which the new findings affect the conclusions presented in the earlier SBU review. The new findings have only a minor impact on the previous conclusions. In some cases, the scientific evidence has become stronger (risk for breast cancer from long-term treatment), while in other cases the uncertainty identified in the earlier report remains (effect on cardiovascular disease and stroke).

CONCEPTS RELATED TO ESTROGEN TREATMENT

The earlier report used the term *estrogen treatment* as a general expression for treatment with hormones during and following menopause (the final menses). In the international scientific literature, and in general discussion, this term is increasingly being replaced by the American concept of *hormone replacement therapy (HRT)*. In Sweden and in most Western nations, HRT covers routine estrogen treatment where estrogen is administered along with gestagen. In cases where estrogen is administered alone, the abbreviation *ERT (estrogen replacement therapy)* is used. These internationally accepted terms are used in this report since they cover the current level of knowledge more broadly than the previous term.

BACKGROUND

Women undergo hormonal change between the ages of 45 and 55 years. The production of female sex hormones successively declines, as does fertility, which eventually ceases completely. An important event in this course is the final menses (menopause).

Symptoms Associated with Menopause

Hot Flashes and Sweating. A high percentage of all women (75%) experience symptoms involving sweating, heat sensation, and hot flashes for several years following menopause. In some cases, these symptoms are hardly noticeable, while in others they can be severe. The symptoms cease spontaneously with time. In some women, symptoms may persist for more than a decade.

Vaginal and Urinary Tract Symptoms. Vaginal and urinary tract symptoms may appear following menopause. Vaginal symptoms include dry or burning sensations, itching, pain during coitus, and transient bleeding or discharge. Urinary tract symptoms may include a burning sensation during micturition, frequent urgency, repeated urinary tract infections, and urinary incontinence. These symptoms are reported to appear in up to one-half of all women during menopause. The symptoms become more common a few years following menopause. Untreated, these disorders can become permanent.

Increased Risk for Health Disorders Following Menopause

Cardiovascular Disease. Myocardial infarction and stroke dominate as causes of morbidity and mortality among Swedish men and women from upper middle age and onward. On average, women experience these problems approximately 10 years later than men do. Female morbidity from these diseases is relatively low prior to menopause. Thereafter, it increases rapidly. This could suggest that estrogen production may offer protection against vascular diseases. However, no direct correlation has been found between the amount of estrogen in the blood and the risk for cardiovascular disease.

The interaction among the effects of estrogen on blood vessels and blood and cardiovascular disease is highly complex. Despite extensive investigation, knowledge in this field remains limited, which motivates further scientific studies.

Osteoporosis and Increased Risk for Fracture. The skeleton also changes following menopause. Throughout life, the skeleton is involved in a dynamic process where the degradation of bone is followed by new bone formation in a well-regulated interplay among the various cells of the skeleton. These cells are influenced directly and indirectly by estrogen. Estrogen deficiency leads to a loss of bone mass, impairs the development of bone structure, and reduces bone strength. This increases the risk for bone fracture, even under moderate stress. The risk increases with increasing age. Fractures of the vertebra

and femoral neck are more common in elderly women than in men, which correlates to the successive decline in estrogen production in elderly women.

Estrogen Agents

Estrogen agents are available in several forms and strengths. Administering low doses—or less active agents—can be sufficient to achieve effects on vaginal and urinary tract symptoms. However, low doses do not have an effect on the heart, vascular system, or skeleton, nor on hot flushes and sweating. Such effects require higher doses or more active agents.

Estriol is an estrogen agent of low potency and is often given for vaginal or urinary tract symptoms. Estradiol is a naturally occurring estrogen agent of moderate potency. It is most commonly used to treat climacteric problems. To date, treatment has usually been given as tablets, but treatment can also be delivered through patches, estrogen gel, or local vaginal treatment. The latter forms act more directly and impact less on the liver, reducing the risk for side effects.

To counteract the risk for cancer in the endometrium, long-term administration of estrogen must be combined with gestagen. The combination of estrogen and gestagen can result in vaginal bleeding and side effects such as a sensation of tension in the breast or mood changes. This may contribute toward not taking the agent as prescribed, i.e., lower compliance.

HRT FOR CLIMACTERIC SYMPTOMS

The most common treatment for climacteric symptoms is estrogen replacement therapy. Long-term estrogen treatment can overstimulate the endometrium and increase the risk for bleeding and, with time, cancer. To counteract these risks, treatment is usually combined with gestagens (HRT).

HRT for climacteric symptoms and vaginal and urinary tract disorders is given only to women with symptoms and not for preventive purposes. In general, treatment does not last more than 5 to 10 years. Low-dose treatment is often given for a longer period to treat problems involving the mucous membranes.

Hot Flushes and Sweating

Controlled studies have shown that different forms of estrogen have good effects on symptoms and quickly relieve problems, for up to 10 years of treatment. Further controlled studies of HRT/ERT have been published since the previous SBU report and show good effects on symptoms. The effect remains as long as treatment continues. It is independent of whether estrogen is given alone (ERT) or in combination with gestagen (HRT). It is also independent of the mode of delivery. Studies also show that HRT does not influence body weight.

Recently, substances have been developed with effects similar to those of estrogen, but they have been studied to a relatively minor extent. The same applies to other hormone combinations, such as estrogen-androgen.

Vaginal and Urinary Tract Symptoms

Treatment with low dose estrogen has good effects on vaginal or urinary tract symptoms. Treatment can be delivered locally. Also, treatment appears to reduce the risk for repeated urinary tract infections. Treatment is also motivated for other urinary tract symptoms such as frequent urgency, urge incontinence, and mixed incontinence. Scientific evidence on the treatment of urinary tract symptoms is more limited than evidence concerning the effects on vaginal symptoms.

Studies published since the previous report have somewhat reduced the uncertainty concerning the effects of HRT on vaginal and urinary tract symptoms.

Life Quality and Mood

Quality of life may decline during menopause, mainly due to the accompanying symptoms. Several new studies on HRT have shown that HRT has positive effects on the quality of life. The extent to which these positive effects override the effects of the special symptoms of menopause is unclear.

HRT AS PREVENTIVE THERAPY

A large part of the new scientific literature addresses the role of HRT in preventing cardiovascular disease, osteoporosis, and fracture. Many major studies have been published, but the results of these studies do not definitively answer the questions.

Preventing Heart Disease

Several studies have attempted to estimate the effects of HRT in preventing heart attacks. Most of the studies concern women who reported regular use of estrogen agents after menopause. These groups were compared to other groups of women who were not treated with estrogen. The groups who received HRT generally had a lower rate of heart attacks or less mortality from heart disease than the control groups. The patient composition in these studies makes it difficult to draw conclusions from the results. These problems have been investigated further since the previous report, and new studies have controlled for several factors that may play a role. This has rendered the assumption, ie, that HRT has preventive effects, less plausible.

A controlled study of HRT in women with previous heart disease has shown that treatment did not reduce the risk for recurrence. Controlled studies of HRT in women without previous symptoms involving the cardiovascular system are under way, but have yet to be published.

It can be noted that the two large American organizations for heart specialists, i.e., the American Heart Association and the American College of Cardiology, reviewed the literature in a report to practicing physicians in the United States during the summer of 2001. They found insufficient evidence to recommend using HRT to prevent the risks for cardiovascular disease in aging women.

Opposed to previous findings, a general assessment of all studies would now suggest that estrogen treatment probably does not protect against myocardial infarction. Further studies are needed to confirm this conclusion. Such studies are under way in the United States and England.

The earlier conclusion—that women who have experienced early menopause, e.g., due to surgical removal of the ovaries, should be treated with estrogen—has not changed.

As in the earlier report, studies aimed at assessing the preventive effects on stroke have not shown any such effects.

The current state of knowledge suggests that HRT should not be used for the specific purpose of preventing cardiovascular diseases.

Preventing fracture

Many factors contribute toward reducing the amount of bone tissue in the skeleton during aging, leading to osteoporosis and a greater risk for fracture. Lowered production of estrogen following menopause leads to a period of more pronounced bone loss. Hence, it is important to study the effects of HRT on bone mass and the incidence of fracture following menopause. The previous SBU report showed that most epidemiological studies found fewer fractures

during ongoing estrogen treatment—the risk fell by nearly half when treatment was started in patients in their 50s, but the effect tended to decline with increased time after the final treatment.

Several studies have been published since, but without resolving the problem. The controlled studies that have been published have presented results that are difficult to interpret and show different effects from HRT in younger and older women. It appears that HRT in younger women helps prevent bone fracture and the loss of bone mass. However, studies that were conducted on older women have not shown the same favorable effects. The question of what impact the duration of treatment has on bone mass or risk for fracture remains.

No studies have yet been published on the effects of HRT in the oldest age groups. The median age for hip fracture in women is somewhat over 80 years. Although bone tissue should react in a similar way at these ages as in younger women, it is plausible that other effects and side effects can differ. For example, how an individual complies with a given prescription plays a role.

The evidence is still unclear regarding the extent to which HRT actually prevents osteoporosis or bone fracture, except in certain risk groups. A project by SBU is currently studying the scientific literature on osteoporosis. A report on this topic will be published in 2003.

Preventing Dementia

Some studies have reported observations that HRT influences general mood and well-being. Hence, it is possible that HRT might prevent, or at least delay, the development of age-related dementia. Some limited studies have shown that HRT may influence cognitive functions, but it is too early to draw any conclusions from these studies.

RISKS ASSOCIATED WITH HRT

Risk for Blood Clots in Veins

Estrogen influences both the coagulation capacity of the body and its potential for dissolving blood clots in the veins. Hence, HRT increases the risk for venous blood clots and possible embolization in the pulmonary arteries.

Recent studies have shown that HRT increases the risk for developing blood clots in veins by two- or three-fold, mainly during the first years of treatment.

Risk for Cancer

Sex hormones affect the breast, endometrium, and ovaries. Growth, maturity, and function are mainly regulated by hormones, primarily estrogen and progesterone. Potential effects from HRT on the risks for breast, uterine, and ovarian cancer have therefore been extensively studied.

Major progress has been made within the area of cancer epidemiology since the last SBU report. It is now possible, with much greater certainty than before, to discuss the relationship between HRT and the incidence of various types of cancer.

Since cancer cannot be viewed as a single disease, and knowledge about the background and incidence of cancer in different organs varies, it is not possible to render a universal judgment on a particular factor's (in this case HRT) impact on cancer incidence generally. Relatively well-founded knowledge is available concerning the increased risk that HRT can represent for breast cancer, uterine cancer, and ovarian cancer.

Some data have also emerged to suggest that some types of cancer appear less frequently in women with HRT than in controlled series.

Breast Cancer. Epidemiological studies addressing the association between HRT and breast cancer clearly show an increased risk for development of breast cancer. This risk appears only after several years of treatment. All of the agents studied increased the risk for breast cancer after 6 to 10 years of treatment. The risk level increases with the duration of treatment time, from 1.5 to 2.5 at 10 to 15 years of treatment. The association between estrogen treatment and breast cancer appears to be highest at or near the time of ongoing treatment. Adding gestagen does not appear to reduce the risk. Some studies show that the types of cancer that appear after estrogen treatment have a less aggressive natural course than tumors that which appear in patients not treated with hormones.

Endometrial Cancer. All of the estrogen agents studied, when administered without gestagen, increase the risk for cancer in the endometrium. This risk is dose dependent and depends on the duration of treatment:

- It increases measurably after 2 to 4 years of treatment;
- It increases successively with the duration of treatment and reaches a tenfold increase after more than 10 years of treatment; and
- It declines after the conclusion of treatment, but some risk remains.

The addition of gestagen reduces risk, and with more continuous treatment it completely prevents increased risk.

Ovarian Cancer. The previous report offered no data on this type of cancer. New studies have been conducted because, in theory, hormone treatment could influence the risk for ovarian cancer.

Some evidence suggests that HRT can increase the risk for this type of cancer after several years of treatment. More studies are needed to confirm this risk.

Colon Cancer. The previous report provided no data on this type of cancer. New studies have been conducted on this type of cancer. There is no evidence of increased risk for colon and rectal cancer following HRT. Rather, some data suggest there are protective effects. However, these data are unconfirmed.

Skin Cancer—Malignant Melanoma. The previous report provided no data on this type of cancer. New studies have been performed on this type of cancer, but the evidence is not conclusive.

Health Economics

The scientific literature provides no evidence for any definitive conclusions concerning the cost-utility of estrogen treatment following menopause. The main reason is that economic studies have included different groups of patients and risk factors, rendering it impossible to assess clinical effects with any certainty.

The cost of estrogen treatment is moderate. Even with relatively minor effects, treatment of symptoms should be cost-effective. This may apply to HRT for climacteric symptoms. More recent and more complex treatment approaches, and new variants of drugs with estrogen effects, should be studied to assess cost-utility, particularly since these agents will probably be more expensive to use.

CONCLUSIONS

- HRT has many advantages, but also some risks. Women themselves—after being thoroughly informed—should decide on the possibility of treatment.
- Treatment using estrogen agents of moderate potency have good effects on the climacteric symptoms of hot flushes and sweating.

Technology assessment reports

- Treating climacteric symptoms during a limited number of years has a confirmed benefit, and none of the scientific evidence shows that it leads to any measurable increase in risk for breast cancer and endometrial cancer, assuming that treatment is designed in accordance with accepted recommendations.
- Treatment using estrogen agents with low potency has good effects on vaginal and urinary tract symptoms.
- There is insufficient scientific evidence to make general recommendations on hormone therapy aimed at prevention in symptom-free women following menopause, although HRT can preserve bone mass around the time of menopause.
- Long-term ERT increases the risk for endometrial cancer, but this increase can be counteracted by the addition of gestagens.
- Longer treatment periods are associated with a risk for breast cancer. The risk depends on the duration of treatment, but it is moderate even in long-term treatment. The potential benefits of HRT must be balanced against the risks; hence, it is important to thoroughly inform women who are deciding about treatment.

It may be difficult to explain why the risk for breast cancer increases from HRT. The magnitude of this risk during and following treatment should be studied in terms of the difference in absolute risk between no treatment and treatment. It is estimated that the risk for developing breast cancer from age 50 to 75 years in women not treated with hormones is 7 cases per 100. This risk can increase to 9 cases per 100 with hormone replacement therapy.

Obesity: Problems and Interventions

BACKGROUND

In recent decades, the percentage of people with obesity has increased markedly in many countries. This trend is observed in most European countries, North America, and several South American and Asian countries.

In Sweden, the number of obese people has nearly doubled during the past 20 years and now totals nearly 500,000. The increased prevalence of obesity applies to both men and women in all age groups. Despite this increase, the prevalence of obesity in Sweden compared to most other countries is relatively low, 8% of the adult population and approximately 6% of children and adolescents. In the United States, for example, the total percentage of the population with obesity is somewhat over 20% while the rates in England, Germany, and Poland exceed 15%.

Definition of Obesity

The cutoff points for overweight and obesity are presented in the Facts box. The definition of obesity that is used most often in a research context is based on body mass index (BMI). Obesity is defined as BMI 30 or more. The measure is based on the combination of height and body weight. In general, men have higher a BMI than women, and in Western nations BMI increases with increasing age in both males and females.

The BMI measure has some deficiencies, particularly as regards obesity in children. It underestimates the degree of overweight in short children and overestimates overweight in tall children. Furthermore, BMI does not consider the relative percentage of fat and muscle,

nor does it reflect the distribution of fat in the body. Clearly, this is a weakness, particularly since research in recent years has shown that the risks for obesity-related diseases are substantially higher when fat is located around the torso and in fat deposits in the abdomen. Waist circumference is a simple and informative measure that reflects total abdominal fat. Another common method is to determine waist circumference in relation to hip circumference, i.e., the waist-to-hip ratio. Both methods are beginning to appear in clinical practice. The measures used most often in the studies reviewed in this report are BMI, or weight reduction in kilograms, or weight reduction as a percent of original weight.

Facts

BMI (Body Mass Index) = body weight in kilograms divided by height in meters squared.
For example:

$$\frac{90\text{kg}}{1.70\text{ m} \times 1.70\text{m}} = 31\text{kg/m}^2 = \text{BMI} = 31$$

Overweight = BMI 25–29.9

Obesity = BMI \geq 30

At the following heights, the lowest weights for obesity are:

160 cm – 77 kg

170 cm – 87 kg

180 cm – 97 kg

Age-adjusted BMI limits are used in children. For example, for a 10-year-old girl the BMI cutoff points would be 20 for overweight and 24 for obesity.

The report defines obesity as BMI 30 or more. Severe obesity is defined here as BMI 35 or more.

The definition of obesity is based on studies of risks for different obesity-related diseases. The risks for serious complications increase markedly at a BMI around 30. There are arguments for, but also against, considering obesity as a disease, which is debated in scientific journals. The project group that worked on the SBU report defines obesity as a disease. However, obesity can exist even without serious complications or disabling conditions. A risk factor does not necessarily lead to disease in the individual case. The SBU Board of Directors, responsible for the introductory summary, has selected to regard obesity as a risk factor and not a disease. This, however, is not intended to tone down the threat that obesity presents to public health.

Causes of Obesity

Research in this field suggests that many different factors are involved in the development of obesity—e.g., genetic, social, behavioral, and cultural, and that these factors influence each other in different ways.

Obesity can develop through a combination of genetic, lifestyle, and environmental factors. The strong role played by genetic factors in this context has been demonstrated in studies of twins and adopted children. Regardless of whether single-egg twins grow up in the same home or in different environments, as adults their body weights and fat deposits are similar. Adopted children develop obesity in the same way as their biological parents rather than their adoptive parents. The genes that regulate this are basically unknown. Various

genetic conditions can, however, help explain why some individuals become obese, but not others who live under the same conditions.

The increase in the prevalence of obesity in Sweden in recent decades cannot, however, be explained by genetic factors, but can be attributed to changes in lifestyle, dietary habits, and physical activity. The risks for becoming obese are greater in societies where there is ample, 24-hour access to fat and energy-rich foods and where the demand for physical activity is low.

Social factors can also influence the development of obesity. Obesity is substantially more common among children and adults who live under disadvantaged socioeconomic conditions.

Health Risks of Obesity

Being slightly overweight does not necessarily cause health problems. Obesity, at least before 64 years of age, clearly increases the risk for disease and premature death. The risk increases with increasing levels of obesity, particularly abdominal obesity. The most common obesity-related complications are type 2 diabetes, high blood pressure, myocardial infarction, gallstones, sleep apnea, joint problems, some cancers, and infertility.

Impact on Quality of Life

Obesity, particularly severe obesity, often has a negative impact on quality of life in both a physical and psychological context. Studies of people with obesity have shown that the health-related quality of life can be very low.

The general stigma against obesity, which can lead to negative and prejudicial attitudes against obese people, often results in major personal suffering and a burden of guilt. No one wants to be obese. The condition is largely genetically driven and triggered by a combination of social, cultural, and community factors that the individual, particularly at a young age, finds difficult to combat.

Economic Aspects

A comprehensive review of international studies addressing the costs of obesity and related complications suggests that the direct healthcare costs may be approximately 2% of the total expenditure for health and medical services. This corresponds to a cost of approximately SEK 3 billion per year in Sweden. In addition, there are the indirect costs due to absence from work and early retirement, which are at least as equally high as the direct healthcare costs.

REPORT DESIGN AND CONTENT

This report reviews the scientific evidence concerning mainly the medical interventions against obesity. The report presents the results found in studies of various strategies for preventing and treating obesity. The evidence presented in the report was obtained through a systematic review of the international scientific literature on the subject. The introductory chapter on the background of obesity as a health problem and the chapter on ethics, however, are not based on a systematic literature review but on a synthesis of other reviews and studies, information from textbooks, questionnaires, and statistical data.

By searching various databases of scientific literature published from 1966 to 2002, the project group identified 2,600 publications that addressed some aspect of interventions against obesity. The systematic review process found that most of these publications were either irrelevant or did not meet the standards established for definition, scientific rigor, and reliability. Some studies used definitions of obesity other than $BMI \geq 30$. Nevertheless,

these were included in cases where it was obvious that many of the study subjects would meet the BMI criteria used to define obesity in the report.

Ultimately, around 300 studies were used to form the conclusions of the report. However, not all are equal in scientific quality. The conclusions were graded (i.e., given an Evidence Grade of 1, 2, or 3) based on the strength of the evidence presented, i.e., depending on study design, the number of subjects included, followup time, and dropout.

The evidence grades are defined as follows:

- Evidence Grade 1: Strong scientific evidence. When at least two studies present evidence of high value.
- Evidence Grade 2: Moderate scientific evidence. When one study presents evidence of high value and at least two studies present evidence of moderate value.
- Evidence Grade 3: Limited scientific evidence. When at least two studies present evidence of moderate value.

PREVENTIVE INTERVENTIONS AGAINST OBESITY

Studies that have investigated the possibilities to influence body weight in a population have so far included relatively limited interventions. Often, the studies have been part of a campaign to reduce high blood pressure, smoking, blood cholesterol levels, and other cardiovascular risk factors. The programs are based on information concerning the importance of suitable diets and increased exercise and other health information directed at a particular group or region. Concurrently, changes in the variables are measured and assessed in a control group or a reference area that did not receive the information. Often, mass media are used for campaigns and newsletters are used for reminders. In some instances, the programs involve professional organizations, voluntary associations, and workplaces. Those recruited for the intervention groups and the control groups are usually examined at the outset of the study and later at specific followup intervals for several years.

Studies on the effects of preventive interventions for children and adolescents are often designed to involve certain schools in providing education, advice, and encouragement toward good dietary habits and physical activity, while other schools are used as control groups.

Preventing Obesity in Adults

Twelve studies met the quality standards outlined in the report. In these studies, the goal was to prevent cardiovascular diseases. Limited attention was given toward counteracting the incidence of obesity. The evidence presented in five studies is of poor quality, mainly because the observation periods were too short or participation in the intervention program was low. Five of the studies provided moderate-grade evidence, and only two of the studies provided high-grade evidence. The Norsjö study (Sweden) did not report any favorable effects regarding the onset of obesity. Similar results were found in five large North American studies. Two of these studies, however, showed that the weight increase that usually occurs in many populations was somewhat less pronounced in cities with the intervention program in contrast to the control cities. In a region in Israel, an ambitious prevention program resulted in a lower prevalence of overweight.

Favorable effects on the prevalence of obesity have not been observed in most population-based prevention programs that have been scientifically assessed.

Preventing Obesity in Children and Adolescents

Thirteen controlled studies were found on this topic. Seven of these provided high- or moderate-grade evidence, and all involved school children aged 5 years or older. Most

included programs to promote physical activity and good dietary habits. Some of the studies also included elements targeted directly at parents. The effects were studied in followup after 2 to 5 years.

Only two of the studies used the most relevant way to measure outcome, i.e., the percentage of children with overweight and obesity. One of these studies found no difference between the trial group and the control group. In the other study, a reduction was achieved in the percentage of overweight girls, but no change was reported among boys in the trial groups. The other studies monitored the mean BMI. This declined in two of the studies, but was not influenced in the other three studies. These conclusions were based on moderate-grade evidence. Overall, a positive result was achieved in three studies, but no effects were reported in four of the seven best studies concerning preventive interventions in children and adolescents. Hence, reliable conclusions cannot be drawn. Several studies noted improved blood lipid levels and reduced blood pressure in the trial groups.

In summary, most of the studies on preventive interventions against obesity have not reported any favorable effects. However, there are examples of programs in both adults and children where up to several kilograms in mean weight reduction has been achieved in the trial areas. Apparently, moderate success in influencing the mean weight in a population can have a major effect on the prevalence of obesity. Therefore, it is particularly important to use well-executed studies to design and assess new strategies adapted to the Swedish population, e.g., through better intervention for establishing good dietary habits in pre-school and school-aged children and by increasing the interest in physical activity in children and adults. Interventions at the national level (e.g., tax and price policies) also need to be tested as a means to reduce the incidence of obesity.

TREATING OBESITY

The fundamental element in all treatment for obesity in both children and adults is changing to a diet with less energy intake. It is essential to limit the fat content. Dietary counseling is often combined with recommendations to exercise regularly to increase energy expenditure. Drugs can be considered as complementary treatment in adults. Treatment using special protein formulas results in a major reduction in energy intake and thereby more pronounced weight reduction in the short term than with other methods.

Weight reduction achieved in this way can have an important impact on an individual's quality of life, morbidity, and future risks. The problem, however, is that obesity often returns. Studies show that most people have regained their original weight after 5 years. However, in some groups of obese patients favorable results have been maintained for several years, particularly if the initial weight reduction was substantial.

To be successful, obesity treatment requires a long-term commitment, and patients must be highly determined and involved. It is a matter of treating a chronic condition that threatens health—not about making cosmetic changes. However, no special measures are needed if the risk is insignificantly higher, such as in people over age 65 years. Earlier treatment strategies have assumed that short-term interventions could have permanent effects. A real problem, however, is to maintain the weight loss which has been achieved during shorter periods, often through different methods and a great deal of effort. It is uncertain whether long-term treatment and followup yield better and more permanent results than the methods that have been studied up to now. It is essential to apply and assess different types of long-term treatment.

Stomach surgery is a treatment alternative that can be considered in cases of severe obesity since substantial and permanent weight loss has been achieved in this patient group.

Treating Obesity in Adults

Dietary Treatment. Dietary treatment involves counseling on the amount and proportions of foods, energy restrictions, limiting fat content with or without energy restrictions, or vegetarian diets. Dietary treatment can also focus on meals and their timing or on replacing meals with formula products.

Twenty-five studies that met the established criteria showed that weight reduction of between 3 kg and 10 kg can be achieved through energy-reduced diets for a 1-year period (Evidence Grade 1). Dietary counseling can be provided to individuals or groups by dietitians or other dietary experts. Replacement of one or more main meals with special products, such as milk or soy-based drinks like those used in VLCD (very low-calorie diets) or “bars” with good nutrient content, can enhance weight reduction (Evidence Grade 2). The few studies that followed weight trends for a longer period, up to 5 years, reported a return to the original weight in most cases (Evidence Grade 2).

Unlimited carbohydrate-rich diets (i.e., at least 50–55 energy percent from carbohydrates and a maximum of 30 energy percent fat, corresponding to 60–75 g fat intake per day) can yield several kilograms weight reduction in 6 months. More pronounced energy restrictions, where fat intake is usually limited to 20–30 grams per day yields more rapid weight reduction, but is more difficult to tolerate for longer periods. Abundant amounts of fruit and vegetables contribute to low fat content and low energy density. A protein rich diet, with more fish, lean meat, and low-fat milk products, appears to promote weight reduction, probably mainly due to an increased satiety. Studies offer no support that lacto-vegetarian diets lead to better weight reduction than mixed diets of the same energy content.

Dietary fiber is a constituent element in the diet. Three studies—two providing poor and one providing moderate evidence, assess the effects of special dietary fiber supplements. The difference between the treatment and control groups was, at most, a few kilograms over 6 to 12 months, but the conclusions are uncertain. There are no studies of long-term effects. In general, dietary advice in Sweden states that fiber intake should be increased due to other health-promoting effects, which also applies to weight reduction.

Very Low-Calorie Diets. Low energy diets, very low-calorie diets (VLCD) are protein-rich formulas manufactured mainly from milk or soy. Dietary recommendations are met by adding essential fatty acids, minerals, and vitamins. VLCD can be used for several weeks as the only source of energy, or to replace some meals.

Common treatment periods using VLCD are 12 weeks or, in some cases, up to 16 weeks. Eight randomized studies have been identified. Initially, substantial weight reduction is achieved, often 15 kg to 20 kg, which is more than with conventional energy-reduced diets. There is a strong tendency to return to the original weight after the treatment, however. Studies for 1 to 2 years, where VLCD has been used intermittently for shorter periods, reported a maintained weight reduction of a few kilograms more than with conventional dietary treatment (Evidence Grade 3).

Starvation was used during the 1960s and 1970s as a treatment for severe obesity. The method involves one or more weeks of total fasting, except for liquids, minerals, and vitamins. The scientific evidence for starvation treatment is weak, and this method is no longer used mainly because muscle mass also declines sharply during starvation.

Behavioral Therapy. Behavioral therapy is used as a component in various types of treatment, but it is difficult to isolate its effects. The effects of different types of behavioral therapy have been analyzed in three randomized controlled studies. In one study (high-grade evidence), various behavioral therapies in combination with different forms of dietary counseling/treatment led to weight loss that was moderate, but significantly greater than in the control group. In two other studies (moderate-grade evidence), no significant differences

were found in weight loss after 1 to 2 years in comparison to the control groups. Firm conclusions, however, cannot be drawn.

Physical Activity. In the studies reviewed, increased physical activity has consisted mainly of walking and, to some extent, jogging in younger individuals. Four studies, whereof two provide good evidence, highlight the effects of physical exercise as a supplement to traditional dietary treatment. A major weight reduction, on average about 4 kg within 1 year, could be achieved in exercise programs compared to the control group (Evidence Grade 1).

Increased physical activity as the only intervention against obesity is substantially less effective than normal dietary treatment (Evidence Grade 3). It cannot be confirmed whether regular physical activity can counteract the weight increase that usually occurs within 1 to 2 years after successful weight reduction.

Pharmacologic Treatment

In Sweden, two drugs are currently approved for weight reduction, orlistat (Xenical[®]) and sibutramine (Reductil[®]). This report reviews nine drug studies. Six of the studies address orlistat treatment and include approximately 2500 patients on active therapy. They are based on moderate evidence as regards the effects after 1 year of treatment. Two of the four studies, that report results after 2 years, provide poor evidence due to high dropout. On average, weight reduction after 1 year was 8 kg (6–10 kg) after treatment with orlistat and 5 kg (4–6 kg) in groups treated with placebo—on average 3 kg more with pharmacological treatment after 1 year (Evidence Grade 2).

Three studies of sibutramine (approximately 1400 actively treated) all provide moderate evidence. After approximately 1 year, two studies with sibutramine show approximately 4 kg greater weight reduction than in the placebo groups. In the largest study, weight reduction after 2 years was more than 5 kg greater than in the control group (Evidence Grade 2).

The side effects associated with orlistat are linked to the active mechanisms of the drug. Diarrhea after intake of too much fat is an expression of deficient compliance with dietary advice. Sibutramine lowers blood pressure less than what would be expected by the weight reduction. Other side effects include sleep disorders, mouth dryness, and constipation.

Both orlistat and sibutramine treatment show weight reduction of 2 kg to 5 kg more than in the control group in treatment up to 2 years. Both drugs yield a weight reduction of at least 10% in one fourth to one fifth of the patients who started treatment compared to half as many in the placebo group. None of the published drug studies report a treatment time exceeding 2 years. The effects on obesity-related morbidity and mortality are unknown.

Surgery. Surgical treatment may be appropriate for severely obese individuals, but only after other treatment attempts have failed. BMI > 40 is generally accepted as a cutoff point for surgery. In special cases, surgery can be appropriate even at a somewhat lower degree of obesity. Seventeen randomized studies and numerous long-term followups (at least 5 years) were assessed. Fifteen nonrandomized, comparative studies contribute to the conclusions as do some results from an ongoing nonrandomized, but controlled, matched study (the Swedish Obese Subjects—SOS study). The SOS study compares 2000 individuals treated by surgery with an equally large control group given routine treatment in primary care.

Over 10 different surgical methods are available to treat obesity, and there are several variants of these methods. Of the surgical methods used in Sweden, gastric bypass has the strongest scientific documentation and the best effect on weight reduction (Evidence Grade 1).

Surgical treatment of individuals with severe obesity yields greater weight reduction than the nonsurgical methods that have been assessed in this patient group. Up to 5 years

following surgery, weight reduction is 50% to 75% of the overweight prior to surgery, which means 30 kg to 40 kg in individuals weighing 125 kg and with a height of 170cm (Evidence Grade 1). A 10-year followup of the SOS study showed that the retained weight loss was, on average, 16% of the original weight. This corresponds to an average of 20 kg in permanent weight loss 10 years after surgical treatment. No weight loss was reported in the control groups.

Weight loss has a positive effect on health-related quality of life (Evidence Grade 2). With major weight loss following surgery, the number of new diabetes cases falls dramatically, and blood sugar levels are nearly completely normalized in individuals with severe obesity and type 2 diabetes (Evidence Grade 1). It is not known whether weight reduction from surgery for severe obesity leads to reduced mortality or less morbidity from myocardial infarction and stroke. In any case, compared to the control groups, surgical treatment for obesity does not increase total mortality during 8 to 10 years. Mortality in conjunction with surgery in Sweden is below 0.5%, and complications during the first episode of care appear in up to 15%. In approximately 2% of new surgery cases, the complications are severe enough to require acute reoperation.

In people with severe obesity, surgical treatment has positive, well-documented long-term effects on weight, quality of life, and morbidity from diabetes.

Alternative Medicine. A relatively large number of methods and agents to treat obesity are available outside of the ordinary healthcare system. Examples include acupuncture, aroma therapy, caffeine, hypnosis, chromium, and vinegar.

More than 500 articles on alternative treatment methods were identified. A thorough review was conducted of the 80 (approx.) articles that are based on studies and describe over 20 treatment alternatives. Eleven of the studies met the minimum criteria for scientific documentation. They included acupuncture, hypnosis, aroma therapy, and chromium-enhanced dietary supplements. The overall judgment was that evidence is lacking on the effects of using alternative methods to treat obesity.

Treating Obesity in Children and Adolescents

Twenty studies that met the minimum criteria were found on treatment with diet, exercise, and behavioral modification. Three studies compared the treatment groups to control groups that received no treatment. The treatment groups reported a weight loss of approximately 10% while the control groups varied in weight between $\pm 3\%$ for the first study year (Evidence Grade 3). Five studies examined long-term followup 3 to 10 years after treatment. Some of these studies found some, albeit weak, retained weight loss, while this could not be observed in other studies. The evidence is insufficient to draw conclusions.

In extremely overweight adolescents, surgery has shown positive treatment results, but the deficiency of adequate studies makes it impossible to draw reliable conclusions. VLCD treatment can also be applied in children and adolescents, but the value of this treatment for longer than a few months cannot be assessed. Rapid weight loss can influence height growth, at least in a 1-year perspective. Studies have reported elevated self-esteem following successful treatment and lowered self-esteem following treatment failure.

QUALITY OF LIFE

Probably the most important reason why obese individuals attempt to lose weight is the negative impact of obesity on the quality of life. This refers to how people feel and function in daily life and the effects that weight-loss treatment can have. Quality of life measurements can provide information on this issue, and we found 27 studies on the topic in the scientific literature.

Clearly, a lower quality of life is perceived by obese individuals compared to the population on average, e.g., as regards physical function, general health status, and vitality (Evidence Grade 1). The association is stronger than for other concurrent morbidity, with more pronounced obesity and if the individual seeks health care (Evidence Grade 2). In many cases, quality of life is lower in those with severe obesity than in patients with other severe chronic diseases (Evidence Grade 3).

Quality of life improves with weight loss. The greater the weight loss, the better the quality of life (Evidence Grade 2). Substantial improvements have been measured in individuals with severe obesity who received surgery and maintained a substantial, long-term weight loss (Evidence Grade 2). Uncertain short-term effects on quality of life for less than 1 year are reported, but the evidence is insufficient to draw conclusions.

EFFECT OF WEIGHT LOSS ON OBESITY-RELATED DISEASES AND CONDITIONS

Weight loss of 5 kg to 10 kg in obese or overweight individuals who also have type 2 diabetes results in improved blood glucose control, usually for 6 months to a maximum of 12 months (Evidence Grade 3). Thereafter, the effects are modest, which is partly attributed to the failure to maintain weight loss, but also to the natural course of diabetes. With the substantial and permanent weight reduction that can be achieved by surgery in individuals with severe obesity, a large percentage of patients have a normal blood glucose level and can discontinue taking medication (Evidence Grade 2).

Using a simple method (glucose tolerance test) it is possible to identify the obese individuals who are particularly at risk for developing type 2 diabetes. Two well-executed studies have shown that moderate weight reduction in combination with physical activity for 2 to 3 years can reduce by half the onset of type 2 diabetes (Evidence Grade 1).

In overweight or obese individuals with moderately elevated blood pressure, a weight loss of approximately 5% is sufficient to achieve a blood pressure reduction for approximately 6 months (Evidence Grade 2). Routine treatment with antihypertensive drugs is, however, more effective even during this period. Despite permanent weight loss after surgery, there is no difference in blood pressure compared to untreated controls in long-term followup.

Effects on blood lipids are related to the extent of weight reduction. When accompanied by weight loss that can be maintained for more than one year, dietary treatment results in some increase in "good" HDL cholesterol which helps diminish arteriosclerosis (Evidence Grade 3). A weight loss of 20 kg to 30 kg is required to reduce the blood level of cholesterol (Evidence Grade 2).

A reduction in sleep apnea has been reported following surgery for obesity. This effect has not been reported in studies of non-surgical treatment methods.

Some studies suggest that weight reduction is an effective treatment method for normalizing hormones, increasing fertility, and improving pregnancy outcomes in women with obesity and menstrual disorders. However, available studies do not permit reliable conclusions to be drawn.

COST-EFFECTIVENESS OF DIFFERENT TREATMENT METHODS

Fourteen assessment studies were reviewed. Five studies address dietary treatment, behavioral therapy, and VLCD. One of these shows that dietary counseling with a dietician alone or dietician and physician resulted in weight loss at a low cost. The results apply after 1 year of followup. Another study shows that behavioral therapy can reduce weight at a low

cost. The cost for VLCD, or a combination of behavioral therapy and VLCD, appears to be somewhat higher.

Several health economic model analyses show that surgical treatment yields a reduction in weight at a relatively low cost. According to three Swedish studies the total cost for surgery and followup during a 4- to 6-year period after surgery is approximately SEK 70,000 higher than in the control group where no weight loss was reported. Related to the percentage of weight loss in the SOS study (16% after 6 years), the costs exceed SEK 4,000 (1994 monetary value) per percent of weight reduction. No further conclusions can be drawn concerning the cost-effectiveness of surgical treatment for obesity.

A health economic assessment has been published concerning pharmacological treatment using orlistat for obesity. This study considered improved life quality from weight reduction. The overall benefit experienced by patients from improved quality of life after 2 years of follow-up was converted to the number of years of full health, i.e., quality-adjusted life-years. The results show that the direct costs slightly exceed SEK 600,000 per quality-adjusted life-year. This would suggest that pharmacological treatment with orlistat has relatively low cost effectiveness. However, due to the weak scientific documentation it is difficult to draw reliable conclusions.

CONCLUSIONS BY SBU

1. *Incidence of obesity and its complications are increasing rapidly.* The number of obese individuals (both adults and children) has increased rapidly during the past 20 years. In Sweden, approximately 500,000 people are defined as obese. Obesity—particularly that localized to the abdomen—increases the risk for many serious diseases, e.g., diabetes, cardiovascular diseases, and joint diseases. The association between obesity and some cancers is strong. Obesity—particularly severe obesity—also has a strong negative impact on the quality of life.
2. *Causes of obesity are only partly known.* The development of obesity depends largely on genetic factors. The inherited predisposition for obesity is widespread in the population. In genetically predisposed individuals, factors related to lifestyle (diet and exercise) and social, behavioral, cultural, and community factors determine whether or not obesity develops.
3. *It is difficult to prevent obesity.* Most population-based prevention programs that have been scientifically assessed have not shown any favorable effects on the prevalence of obesity. However, examples exist of programs for both adults and children that have been successful, at least in the short term. New strategies to disseminate knowledge about the causes and risks of obesity and to change dietary habits and motivate people to increase physical activity need to be developed and assessed. Concurrently, there is a need for policy interventions at the societal level to reduce the prevalence of obesity.
4. *Scientific assessment of treatment methods for obesity shows that:*
 - Changing dietary habits through successful dietary counseling (mainly reducing energy and fat intake) can lead to weight loss, as a rule 3 kg to 10 kg during the first year (or 10% of body weight in children). The long-term effects are uncertain;
 - Regular exercise contributes to weight reduction;
 - Behavioral therapy in conjunction with changes in diet and exercise can yield further effects on weight if the supportive interventions are continued for a longer period;
 - Approximately one-fifth of those treated according to Weight Watcher methods achieve a permanent weight loss of 10% or more of their starting weight;
 - VLCD for 6 to 12 weeks yields a greater weight loss than a conventional low energy diet. In studies of VLCD for 1 to 2 years, where treatment often has been periodic, researchers have noted a maintained weight loss of a few kilograms more than in treatment with a balanced diet alone (VLCD = Very Low Calorie Diets, i.e., protein-rich formula);

- Pharmacological treatment with orlistat (Xenical®) or sibutramine (Reductil®) yields an average 2 kg to 5 kg weight loss beyond that achieved with diet and exercise counseling alone. In clinical trials, one-fourth to one-fifth of those who started pharmacological treatment lost at least 10% weight compared to half as many in the group treated with placebo;
 - The major problem is that weight loss is usually not permanent. Within a few years most of those who initially succeeded in losing weight had returned to their original weight. Therefore, it is particularly important to develop and assess long-term treatment aimed at permanent weight reduction;
 - Surgical treatment, which can be appropriate for patients with severe obesity, lowers weight on average by more than 25% (eg, from 125 kg to 90 kg) up to 5 years after surgery. After 10 years, the retained weight loss is approximately 16%, or on average somewhat over 20 kg. This represents substantial gains in health and quality of life in these patients. However, surgical intervention carries some risk for complications; and
 - The scientific evidence for a wide range of alternative medicine methods is too weak to draw any reliable conclusions about the possible effects these methods may have on obesity.
5. *Risks related to obesity can be reduced.* The risks related to obesity can be reduced through weight reduction, regardless of the methods used. Intervening against other risk factors—even if weight reduction is not successful—can reduce the risks associated with obesity. Examples of such interventions include increased physical activity, smoking cessation, and improved control of diabetes, high blood pressure, and elevated blood lipids.
 6. *Limited information about cost-effectiveness.* The costs to society for obesity and the diseases associated with obesity are high. Information about the cost effectiveness of different methods is, however, limited. The cost effectiveness of preventive methods cannot be calculated due to uncertainty concerning their effects. In treating obesity, the costs are relatively low for weight loss achieved through dietary counseling, behavioral therapy, dietary replacement formulas with low-energy content, and surgical treatment, but considerably higher for pharmacological treatment. Studies have not calculated cost effectiveness based on the observed reduction in morbidity or mortality or improvements in quality of life.
 7. *Prejudice against obesity must be opposed.* Those affected by obesity should not be treated with negative or prejudicial attitudes—many people are at risk for obesity, but no one wants to be obese. The lower quality of life that people with obesity experience is somewhat related to the attitudes of society. Increased understanding of the reasons for obesity and difficulties in treating it may help to reduce the prejudice against people with obesity that is found both in health services and in society at large.